

Lipid conjugated prodrugs for enzyme-triggered liposomal drug delivery to tumors

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Published in:

American Chemical Society. Abstracts of Papers (at the National Meeting)

Publication date:

2011

Document Version

Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):

Clausen, M. H. (2011). Lipid conjugated prodrugs for enzyme-triggered liposomal drug delivery to tumors. American Chemical Society. Abstracts of Papers (at the National Meeting), 242, MEDI 20.

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Division of Medicinal Chemistry
Scientific Abstracts
for the
24th National ACS Meeting and Exposition
September 1-5, 2011
Denver, CO

Publication date: August 2, 2011

American Chemical Society
Division of Medicinal Chemistry
242nd ACS National Meeting, Denver, CO, August 28 - September 1, 2011

J. Barrish, Program Chair

SUNDAY MORNING

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siRNA

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First Time Disclosure of Clinical Candidate

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J. Kenny, Organizer; J. Kenny, Presiding Papers 381-385

MEDI 1

WITHDRAWN

MEDI 2

Discovery of phosphodiesterase-10 (PDE10) inhibitors for the treatment of schizophrenia

Izzat T Raheem¹, izzat_raheem@merck.com; Jim Barrow²; Rodney A Bednar³; Michael J Breslin¹; Joseph Bruno³; Victoria Cofre³; Paul J Coleman¹; Christine Fandozzi⁴; Joy Fuerst⁵; Lisa Gold⁶; Nicole Hill⁵; Pete H Hutson⁶; Sarah Huszar⁷; Monika Kandebo⁶; Amanda Kemmerer³; Somang H Kim⁴; Raghu Krishnan³; Wei Lemaire³; Bennett Ma⁴; Georgia McGaughey⁸; Sanjeev Munshi⁹; Shannon Nguyen⁷; Sophie Parmentier-Batteur⁶; John D Schreier¹; Sujata Sharma⁹; William D Shipe²; Sean Smith⁶; Jason Uslaner⁷; Youwei Yan⁹; Christopher D Cox¹. (1) Program Team Chemistry, Merck & Co., Inc., West Point PA 19486, United States (2) Automated Synthesis and Purification, Merck & Co., Inc., West Point PA 19486, United States (3) In Vitro Sciences, Merck & Co., Inc., West Point PA 19486, United States (4) Drug Metabolism, Merck & Co., Inc., West Point PA 19486, United States (5) Basic Pharmaceutical Sciences, Merck & Co., Inc., West Point PA 19486, United States (6) Neurosymptomatology, Merck & Co., Inc., West Point PA 19486, United States (7) In Vivo Pharmacology, Merck & Co., Inc., West Point PA 19486, United States (8) Chemistry Modeling and Informatics, Merck & Co., Inc., West Point PA 19486, United States (9) Structural Chemistry, Merck & Co., Inc., West Point PA 19486, United States

Schizophrenia is a chronic and debilitating neurological disease with onset typically occurring during early adulthood. The disease is characterized by a combination of positive (hallucinations), negative (anhedonia, social withdrawal), and cognitive symptoms, and is estimated to affect 1% of the global population. While currently marketed "typical" and "atypical" therapeutics exist, they are prone to an array of adverse events (AEs), often resulting in discontinuation due to poor efficacy and/or tolerability. As such, alternative pharmacological approaches toward treating schizophrenia represent an unmet medical need. The phosphodiesterases (PDEs) are a superfamily of 11 enzymes responsible for the hydrolytic degradation of the second messengers cAMP and cGMP. Specifically, PDE10 is highly expressed and localized in the mammalian striatum, and is implicated in the regulation of cyclic nucleotide signalling cascades that intersect both the glutamatergic and dopaminergic pathways regulating behavioral control. As such, inhibition of PDE10 is hypothesized to represent a mechanistically novel approach toward the treatment of schizophrenia, and recent preclinical results support this hypothesis. We describe the discovery and development of potent and orally bioavailable tetrahydropyridopyrimidine inhibitors of PDE10 obtained by systematic optimization of a proprietary Merck HTS lead. Leading compounds exhibit sub-nanomolar potencies, excellent pharmacokinetic (PK) properties, and clean off-target profiles. These inhibitors display *in vivo* target engagement as measured by both an *ex vivo* occupancy assay and increased striatal

cGMP levels upon oral dosing. They also display dose-dependent efficacy in key pharmacodynamic (PD) assays predictive of anti-psychotic activity, including the psychostimulant-induced rat hyperlocomotion assay and the conditioned avoidance response assay.

MEDI 3

Discovery of JNJ-42601572, a γ -secretase modulator with potent, central activity in mouse and dog

Francois Bischoff, *fbischof@its.jnj.com*; **Harrie Gijzen**, *hgijzen@its.jnj.com*; *Didier Berthelot; Michel De Cleyn; Gregor Macdonald; Daniel Oehlich; Michel Surkyn; Andres Trabanco; Gary Tresadern; Sven Van Brandt; Adriana I Velter; Herman Borghys; Chantal Masungi; Marc Mercken. Department of Neuroscience, Janssen Research & Development, Beerse B-2340, Belgium*

Accumulation of neurotoxic amyloid-beta 42 peptides (Ab42) in the brain is a hallmark of Alzheimer's disease (AD). Gamma-secretase, an intramembrane-cleaving protease responsible for the production of amyloid-beta peptides, has emerged as an important target for the development of novel therapeutics for AD. γ -Secretase modulation rather than plain inhibition has been postulated to be an alternative strategy to intervene pharmacologically within the amyloid cascade. It causes a product shift at the expense of Ab42 to the shorter, more soluble and less amyloidogenic Ab38 without inhibiting NOTCH proteolytic processing. The design and the synthesis of several chemical subclasses of *in vitro* and *in vivo* potent γ -secretase modulators (GSM) will be presented as well as their drug-like properties. This study has led to the identification of our lead compound, JNJ-42601572 which, in a non-transgenic mouse brain, upon oral dosing (30 mg/kg, 4 h) induces a 63% lowering of Ab42 levels and a 91% increase of Ab38 levels with unchanged total levels of amyloid peptides. Moreover, JNJ-42601572 elicits very potent *in vivo* activity across species as it induces upon oral dosing (20 mg/kg, 8 h) a 60% lowering of Ab42 levels and a 60% increase of Ab38 levels in dog cerebrospinal fluid.

MEDI 4

Discovery of a series of brain-penetrant kynurenine aminotransferase II inhibitors for the treatment of schizophrenia

Amy B. Dounay, *amy.dounay@pfizer.com*. *Neuroscience Medicinal Chemistry, Pfizer Worldwide Research and Development, Groton CT 06340, United States*

Kynurenine aminotransferase (KAT) II has been identified as a potential new target for treatment of cognitive impairment associated with schizophrenia. Following a high throughput screen, cyclic hydroxamic acid PF-04859989 emerged as a lead compound for the program. PF-04859989 represents the first reported brain penetrant tool compound for KATII. Additionally, our studies revealed that PF-04859989 inhibits KATII

irreversibly by forming a covalent adduct with co-factor pyridoxal phosphate (PLP) in the enzyme active site. Key challenges for the medicinal chemistry team included developing a clear understanding of the structural features affecting the irreversibility of inhibition and design of compounds with potency at both rat and human KATII isozymes. X-ray crystallography, homology modeling, and biophysical studies to probe irreversibility have been critical components of the team's design strategy. Additionally, protein NMR experiments with ^{13}C -labeled PF-04859989 have provided deeper insight into the mechanism of irreversible inhibition. Highlights of these studies and their impact on the team's lead optimization efforts will be described.

MEDI 5

Design and synthesis of Benzimidazole based inhibitors of Raf kinase: A med. Chem approach towards the discovery of Phase II clinical candidate RAF265

Savithri Ramurthy¹, savithri.ramurthy@novartis.com; Payman Amir²; Abran Costales¹; Johanna M Jansen¹; Barry Levine³; Sylvia Ma²; Christopher M McBride³; Teresa Pick⁴; Daniel J. Poon¹; Cynthia M. Shafer¹; Darrin Stuart²; Leonard Sung³; Ahmad Hashash⁵; Paul Renhowe¹; Eleni Venetsanakos²; Jeremy Murray³; Brent Appleton¹; Mina Aikawa²; Joelle Verhagen³; Kimberly Aarderlin². (1) Global Discovery chemistry / Oncology and Exploratory Chemistry, Novartis Institutes for Biomedical Research, Emeryville CA 94608, United States (2) Oncology, Novartis Institutes for Biomedical Research, Emeryville CA 94608, United States (3) NA, United States (4) Lawrence Livermore Laboratories, United States (5) Gilead Sciences, United States

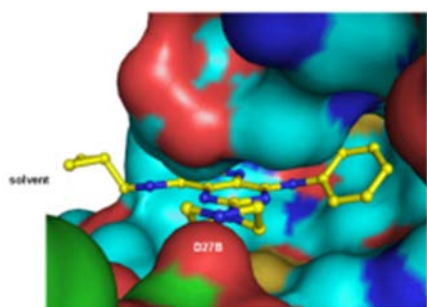
The Ras/Raf/MEK/ERK pathway plays a central role in mediating proliferation and survival signals from the cell membrane to the nucleus and cytoplasm. Activation of this pathway often occurs in cancer cells, the importance of which is underscored by the observation that activating mutations in Ras and B-Raf frequently occur in human cancer. Thus a potent Raf inhibitor could have a significant impact in treating cancers that are dependent on activated Ras or Raf for survival and proliferation signaling. Malignant melanoma represents a promising indication for a Raf inhibitor given the high percentage of B-Raf (60-70%) mutations and the huge unmet medical need. Here, we describe the medicinal chemistry approaches which led to the discovery of Raf265, a novel, orally bioavailable small molecule inhibitor of c-Raf, B-Raf and mutant B-Raf (V600E) that also inhibits VEGFR-2. This target profile provides two potential mechanisms for inhibiting tumor growth: direct anti-proliferative/pro-apoptotic effects on tumor cells through inhibition of Raf, and anti-angiogenic activity through inhibition of VEGFR-2. Design strategy, synthesis and the *in vitro*, *in vivo* activities of the early Benzimidazole analogs and Raf 265 will also be discussed.

MEDI 6

Inhibitors of ketohexokinase: Discovery of pyrimidinopyrimidines with specific substitution that complements the adenosine 5'-triphosphate (ATP) binding site

Bruce E. Maryanoff, bmaryano@scripps.edu; John O'Neill; David McComsey; Stephen Yabut; Diane Luci; Alfonso Jordan; John Masucci; William Jones; Marta Abad; Alan Gibbs; Ioanna Petrounia. Johnson & Johnson Pharmaceutical Research & Development, Spring House PA 19477-0776, United States

Ketohexokinase (KHK; fructokinase) phosphorylates fructose on position C1 with the agency of ATP to yield fructose-1-phosphate, which enters normal metabolic pathways. Attenuation of fructose metabolism by the inhibition of KHK should reduce body weight, free fatty acids, and triglycerides, thereby offering a novel approach to treat diabetes and obesity in response to modern diets. We have identified potent, selective inhibitors of human hepatic KHK within a series of pyrimidino[5,4-d]pyrimidines. Several compounds exhibited KHK IC₅₀ values in the range of 5-20 nM and showed potent cellular KHK inhibition (IC₅₀ < 500 nM), which relates to their intrinsic potency vs KHK and their ability to penetrate cells. X-ray co-crystal structures of ligand•KHK complexes revealed the important interactions within the enzyme's ATP-binding pocket (e.g., see Figure). The structure-activity relationship (SAR) for this pharmacophore will be discussed in the context of our X-ray results.



MEDI 7

Discovery of BMS-626531, a potent and selective inhibitor of p38 α MAP kinase as a clinical candidate for the treatment of inflammatory diseases

Alaric J. Dyckman, alaric.dyckman@bms.com; Tianle Li; John Hynes; Hong Wu; Stephen T. Wroblewski; Shuqun Lin; Chunjian Liu; James Lin; John Wityak; Jagabandhu Das; Robert V. Moquin; Kathleen M. Gillooly; Sidney Pitt; Ding Ren Shen; Rosemary F. Zhang; Kim W. McIntyre; David J. Shuster; Hongjian Zhang; Punit H. Marathe; Arthur M. Dowsyko; John S. Sack; Jingsong Wang; Murray McKinnon; John H. Dodd; Joel C. Barrish; Gary L. Schieven; Katerina Leftheris. Research and Development, Bristol-Myers Squibb, Princeton NJ 08543-4000, United States

The mitogen-activated protein kinase p38 α has been shown to be on the critical path to pro-inflammatory cytokine production (notably TNF- α and IL-1 β). In recent years, biotherapeutic treatments have provided clinical validation for anti-cytokine approaches to treating rheumatoid arthritis, Crohn's disease and psoriasis. Small molecule-based inhibition of p38 α as an alternative approach to block production of these cytokines offers the potential benefits of reduced cost and ease of administration. These aspects,

along with the ability to simultaneously affect multiple cytokines and inflammatory mediators, have stimulated continued efforts to develop safe, potent and orally active p38 α inhibitors. This presentation will describe the structure-based design, synthesis, and structure-activity relationship of a novel series of p38 α inhibitors. A survey of the pharmacokinetic properties of these molecules and their in vivo efficacy in various models of acute and chronic inflammation will be highlighted. The discovery and profile of the clinical development candidate BMS-626531 will be discussed for the first time.

MEDI 8

Identification of novel and selective ITK inhibitors through a template hopping strategy

Aoife C Maxwell, *aoife.c.maxwell@gsk.com*; Catherine Alder; Amanda Campbell; Aurelie Champigny; Martin Ambler; John Harling; Callum Scullion; Ian Smith; Don Somers; Chris Tame; Caroline Wilson; James Woolven. Respiratory CEDD, GlaxoSmithKline, Stevenage Hertfordshire SG1 2NY, United Kingdom

Interleukin-2 inducible Tyrosine kinase (ITK) is a non-receptor protein tyrosine kinase which is expressed in T cells, mast cells and NK cells. ITK plays a role in signalling, downstream of the T cell receptor. Inhibition of ITK potentially constitutes a novel, non-steroidal treatment for asthma and other T-cell mediated diseases. In-house kinase cross-screening resulted in the identification of an aminopyrazole-based series of ITK inhibitors. Initial work on this series highlighted selectivity issues with several other kinases including LCK, AurA and AurB. These issues could not be readily resolved via simple modifications. A template hopping strategy was therefore initiated in order to identify an inherently more selective hinge binder which would still be capable of capitalising on the SAR already developed in the aminopyrazole series. Herein we describe the strategy we used to identify a selective hinge binder, how this resulted in the identification of a novel and selective series of ITK inhibitors and modelling and crystallographic rationale for the observed selectivity.

MEDI 9

Discovery and optimization of a series of benzothiazole PI3K / mTOR dual inhibitors

Noel D D'Angelo¹, *dangelo@amgen.com*; Tae-Seong Kim¹; Kristin Andrews²; Shon K Booker¹; Sean Caenepeel³; Kui Chen⁴; Derin D'Amico¹; Dan Freeman³; Jian Jiang⁵; Longbin Liu¹; John D McCarter⁴; Tisha San Miguel⁴; Erin L Mullady⁶; Michael Schrag⁵; Raju Subramanian⁵; Jin Tang⁷; Robert C Wahl⁴; Ling Wang³; Douglas A Whittington⁷; Tian Wu⁸; Ning Xi¹; Yang Xu⁵; Peter Yakowec⁷; Kevin Yang¹; Leeanne P Zalameda⁴; Nancy Zhang³; Paul Hughes³; Mark H Norman¹. (1) Department of Medicinal Chemistry, Amgen, Inc., Thousand Oaks CA 91320, United States (2) Department of Molecular Structure, Amgen, Inc., Thousand Oaks CA 91320, United States (3) Department of Oncology Research, Amgen, Inc., Thousand Oaks CA 91320, United States (4)

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Phosphoinositide 3-kinases (PI3K's) are a family of lipid kinases that play key regulatory roles in cell proliferation, survival, and cell translation. The mutation or amplification of PI3K- α in humans has been implicated in the growth of multiple tumor types. Consequently, the PI3K's in general and PI3K- α in particular have become targets of intense research for drug discovery. Our studies began with the identification of benzothiazole compound **1** from a high throughput screen. Extensive SAR studies led to the discovery of sulfonamides **38** and **45** as early leads, based on their *in vitro* cellular potencies. Subsequent modifications of the central pyrimidine ring dramatically improved enzyme and cellular potency and led to the identification of chloropyridine **70**. Further aryl sulfonamide SAR studies optimized *in vitro* clearance and led to the identification of **82** as a potent dual inhibitor of PI3K and mTOR. This molecule exhibited potent enzyme and cell activity, low clearance, and high oral bioavailability. In addition, compound **82** demonstrated tumor growth inhibition in U-87 MG, A549, and HCT116 tumor xenograft models.

MEDI 10

Discovery of potent and highly selective PI3-Kinase Delta inhibitors: Taming time-dependent inhibition

Brian S Safina, bsafina@gene.com. *Discovery Chemistry, Genentech Inc., South San Francisco CA 94080, United States*

PI3K- δ is a lipid kinase and a member of a larger family of enzymes, PI3K Class IA(α , β , δ) and IB (γ) that catalyze the phosphorylation of PIP2 to PIP3. PI3K δ is mainly expressed in leukocytes, where it plays a critical, non-redundant role in B cell receptor mediated signals and thus, provides an attractive opportunity to treat rheumatoid arthritis. We report the discovery of novel, potent and selective PI3K δ inhibitors and describe our hypothesis for isoform (α , β , γ) selectivity gained from interactions in the affinity pocket. The critical component of our initial pharmacophore was implicated in causing CYP3A4 time-dependant inhibition (TDI) and strategies, such as diverting metabolism, MetID and key SAR will be presented in detail. Ultimately, a structure-based design approach was employed to identify a suitable drug-like replacement for further optimization. The results of those efforts will be disclosed in the subsequent talk.

MEDI 11

Designer lipids for cytoplasmic delivery of nucleic acids

Francis C. Szoka, PhD., szoka@cgl.ucsf.edu. Departments of Bioengineering, Therapeutic Sciences & Pharmaceutical Chemistry, University of California, San Francisco CA 94143-0912, United States

We have synthesized a family of zwitterlipids that are pH and/or enzyme responsive that form liposomes at pH 7.4 and efficiently encapsulate nucleic acids. The liposomes were used to explore the lipid chemical-attributes that control cytoplasmic delivery of the liposomal contents. Both classes of lipids, pH and enzymatically triggered, become positively charged upon triggering. The pKa of the zwitterlipid and lipid acyl chain composition are critical to obtain significant levels of siRNA transfer using an *in vivo* factor VII knockdown assay in mice. Adverse effects such as the induction of inflammatory mediators was minimal for most lipids studied. Supported by NIH EB03008 & Pfizer, Inc.

MEDI 12

pH-Responsive polymeric carriers for siRNA drug delivery

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RNA drugs have significant therapeutic potential, but effectively formulating and delivering them remains a widely recognized challenge. We have been developing synthetic polymeric carriers that mimic the highly efficient intracellular delivery systems found in pathogenic viruses and organisms. Their most important property ties together the sensing of pH changes to membrane destabilizing activity, and the carriers thus possess a hidden functionality that is expressed in the endosomal compartment to increase cytosolic delivery of macromolecules. Another important aspect of these polymeric carriers is the development of controlled polymerization techniques to streamline bioconjugation of targeting agents, as well as to generate controlled carrier architectures. Optimization of architecture and delivery activity has led to carriers with excellent efficacy and pharmaco-kinetic properties.

MEDI 13

siRNA delivery using PRINT particles

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The PRINT platform enables unprecedented control over particle size, shape, composition, deformability, surface chemistry and cargo loading. Two different matrices are being explored for siRNA delivery: PLGA and PEG hydrogels. The PLGA matrix utilizes a non-polyplex forming method to deliver siRNA while a cleavable siRNA

'prodrug' approach is being developed for the PEG hydrogel system. Targeting is being achieved by coating the particles with different ligands that can physisorb to the particle surface. Various disease models are being investigated for the application of the siRNA-containing PRINT particles.

MEDI 14

Liposome and polymer conjugate delivery of siRNA

Steven L. Colletti, *steve_colletti@merck.com. Department of Medicinal Chemistry, Merck & Co., Inc., West Point PA 19486, United States*

The recent field of RNA interference (RNAi) continues to grow and evolve at a rapid pace toward the realization of therapeutics. An important key to the discovery of RNAi therapeutics, is the safe and effective delivery of short interfering RNA (siRNA). Merck and Co. entered the field with the acquisition of Sirna Therapeutics, and has since developed multiple platforms for siRNA delivery. Medicinal chemistry design has been at the core of these delivery strategies. This presentation will highlight some of the advances in lipid nanoparticle and polymer conjugate delivery of siRNA. The application of medicinal chemistry principles, such as structure activity relationships (SAR), will be featured, as well as issues of absorption, distribution, metabolism, excretion, and toxicity (ADMET).

MEDI 15

Potent and highly selective benzimidazole inhibitors of PI3-Kinase delta

Zachary K Sweeney, *sweeney.zachary@gene.com. Small Molecule Drug Discovery, Genentech, Inc., South San Francisco California 94080, United States*

Inhibition of PI3K δ is considered to be an attractive mechanism for the treatment of inflammatory diseases and leukocyte malignancies. Using a structure-based design approach, we have identified a series of potent and selective benzimidazole-based inhibitors of PI3K δ . These inhibitors do not occupy the selectivity pocket between Trp760 and Met752 that is induced by other families of PI3K δ inhibitors. The pharmacokinetic properties of these compounds and the ability of representative inhibitors to modulate the function of B-cells in vivo will be described.

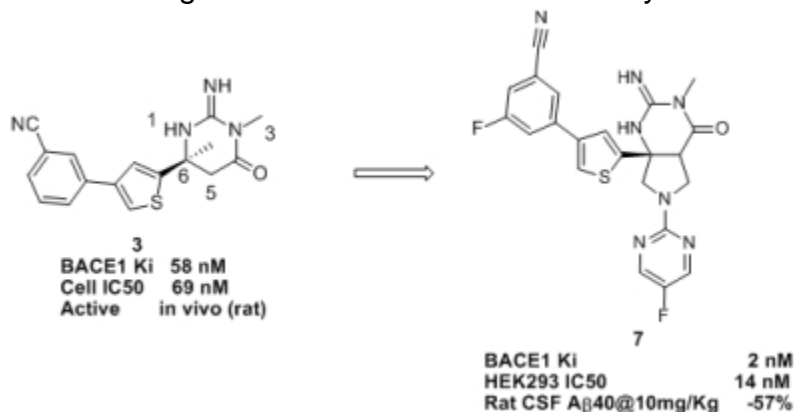
MEDI 16

Discovery and development of pyrrolidinoiminopyrimidinones as potent and selective BACE1 inhibitors

Johnny Zhu¹, *johnnyzzhu@msn.com*; Xiaoxiang Liu¹; Mihirbaran Mandal¹; Robert Mazzola¹; James Durkins¹; John Caldwell¹; Johannes Voigt²; Corey Strickland³; Mathew Kennedy⁴; Xia Chen⁴; Reshma Kuvelkar⁴; Prescott Leach⁴; Michael Grzelak⁴; Lynn

Hyde⁴; Qi Zhang⁴; Giuseppe Terracina⁴; Lili Zhang⁴; Leonard Favreau⁵; Eric Parker⁴; Brian McKittrick¹; Andrew Stamford¹; Michael Czarniecki¹; William Greenlee¹; John Hunter⁴. (1) Medicinal Chemistry, Merck Research Laboratories, Kenilworth NJ 07033, United States (2) CM&I, Merck Research Laboratories, United States (3) Structural Chemistry, Merck Research Laboratories, United States (4) Neurobiology, Merck Research Laboratory, United States (5) DMPK, SPRI, United States

Alzheimer's disease is caused by widespread neuronal dysfunction and cell death that is believed to be initiated by synaptic deposition of Ab42 oligomers related to their overproduction, decreased clearance or enhanced aggregation. Ab42 is generated from the membrane bound Amyloid Precursor protein (APP) via sequential cleavages first by b-secretase-1 (BACE1) followed by g-secretase. BACE inhibition has been viewed as an attractive path for potential treatment of Alzheimer's disease through reduction of Ab42 production. A unique structural class of cyclic acylguanidine BACE inhibitors has been designed and validated as highly potent and selective and CNS penetrant BACE inhibitors, starting from a fragment based protein NMR screening lead with extensive use of X-ray crystallography and CADD technologies. Here we will briefly discuss the in vivo rat efficacy guided SAR work evolving from iminopyrimidinone **3** to **7** through rational design based on conformational analysis.



MEDI 17

Novel kappa opioid peptides with drug-like properties

Jane V. Aldrich¹, jaldrich@ku.edu; Santosh S. Kulkarni¹; Sanjeewa N. Senadheera¹; Nicolette C. Ross²; Kate J. Reilley²; Shainnel O. Eans²; Michelle L. Ganno²; Jay P. McLaughlin². (1) Department of Medicinal Chemistry, The University of Kansas, Lawrence KS 66045, United States (2) Torrey Pines Institute for Molecular Studies, Port St. Lucie FL 34990, United States

Ligands for kappa opioid receptors (KOR) have potential therapeutic application in a number of areas, including in the treatment of pain and drug abuse. A major challenge in developing peptides for these receptors and other targets as potential therapeutic agents has been their metabolic stability and distribution following systemic administration. The novel cyclic tetrapeptide CJ-15,208 was reported to be a KOR

antagonist *in vitro* (Saito *et al.*, *J. Antibiot.* **2002**, 55, 847). Because of its cyclic structure this peptide was expected to be resistant to proteolytic degradation and potentially systemically active. Therefore we synthesized this peptide (Ross *et al.*, *Tetrahedron Lett.* **2010**, 51, 5020) along with a number of analogs and evaluated selected peptides *in vivo*. Unexpectedly the lead peptide exhibited analgesic activity in the 55°C warm water tail withdrawal assay in mice following systemic (intraperitoneal) administration (ED₅₀ (and 95% confidence interval) = 4.5 (1.2-20.3) mg/kg). Characterization in additional *in vivo* assays indicated that this peptide is a mixed agonist/antagonist and suggests that it could be a potentially clinically useful analgesic with decreased liabilities compared to current narcotic analgesics (e.g. morphine). Analogs of the lead peptide exhibited different pharmacological profiles *in vivo* in terms of agonist activity and the opioid receptors involved. An analog that exhibits primarily KOR antagonist activity *in vivo* is also systemically active and blocks stress-induced reinstatement of cocaine seeking behavior. These cyclic peptides represent significant advances in the development of potential peptide therapeutics for KOR. Research supported by NIDA grants R01 DA018832 and DA023924.

MEDI 18

Discovery of novel small molecule Mer kinase inhibitors for the treatment of pediatric acute lymphoblastic leukemia

Xiaodong Wang¹, xiaodonw@unc.edu; Jing Liu¹; Chao Yang¹; Catherine Simpson¹; Amy Deusen¹; Jacqueline Norris-Drouin¹; William Janzen¹; Dmitri Kireev¹; Stephen Frye¹; Deborah DeRychere²; Doug Graham²; Debra Hunter³; H Shelton Earp³. (1) Division of Medicinal Chemistry and Natural Products, University of North Carolina, Chapel Hill NC 27599, United States (2) Department of Pediatrics, University of Colorado at Denver, Aurora CO 80045, United States (3) Department of Medicine and Pharmacology, University of North Carolina, Chapel Hill NC 27599, United States

Ectopic Mer expression in T-cell acute lymphoblastic leukemia (ALL) is suspected to be responsible for drug resistance in children and Mer kinase inhibitors may act as chemosensitizers to increase efficacy and reduce toxicities of current regimens in this disease. Based on the known X-ray crystal structure of Mer with **Compound 52**, a rational structure-based design approach was applied to discover novel small molecule Mer inhibitors. A strong structure-activity relationship (SAR) has been built up within the Tyro-3, Axl, and Mer family of receptor tyrosine kinases for the pyrazolopyrimidine scaffold. In the process, Sub-nanomolar Mer inhibitors have been discovered. The lead compound has been evaluated for selectivity against other kinase families with promising results. Optimization of this scaffold toward a clinical candidate is underway.

MEDI 19

Selective small molecule probes for inhibition of breast cancer stem cells

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Cancer stem cells (CSCs), which drive tumor growth, are known to be resistant to standard chemotherapy and radiation treatment. [i] This raises a very significant unmet need to find therapies that can target CSCs within tumors because these cells are responsible for recurrence, the primary cause of patient mortality. However, CSCs are not stable outside the tumor environment and are not easy to grow in culture media. Hence, stable sibling cell lines that were induced into epithelial-to-mesenchymal transdifferentiation (EMT) to stably propagate CSC-enriched populations[ii] were used to screen a library of about 300,000 compounds from the Molecular Libraries Small Molecule Repository (MLSMR). Several classes of selective inhibitors of CSCs were identified. The use of isogenic control cell lines for the secondary validation assays minimized the probability of false hits advancing along the critical path to probe development. Medicinal chemistry efforts on the identified hits resulted in chemical probes with increased potency and selectivity. In addition to advancing the basic research in the biology of CSCs, these small molecule probes are attractive starting points for developing anticancer drugs. [i] Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, Dewhirst MW, Bigner DD, Rich JN. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature* 2006 Dec 7;444(7120):756-60. PubMed PMID: 17051156 [ii] Gupta PB, Onder TT, Jiang G, Tao K, Kuperwasser C, Weinberg RA, Lander ES. Identification of selective inhibitors of cancer stem cells by high-throughput screening. *Cell*. 2009 Aug 21;138(4):645-59. PubMed PMID: 19682730

MEDI 20

Lipid conjugated prodrugs for enzyme-triggered liposomal drug delivery to tumors

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For some time we have been developing novel enzyme-triggered prodrugs for drug delivery targeting cancer. The liposomal prodrugs take advantage of the EPR effect to localize to tumors and of the local over-expression of secretory phospholipase A₂ in tumors. Compared to conventional liposomal drug delivery systems, our prodrug-lipid conjugates have two main advantages: 1) the drugs are covalently linked to the lipids and thus leakage is circumvented and 2) the lipophilic bilayer of the formulated liposomes effectively shields the drugs from the aqueous environment *in vivo*. Consequently, the strategy accommodates therapeutic agents with otherwise

unfavorable pharmacokinetic properties. We have designed and synthesized different prodrugs, including published examples using capsaicin, chlorambucil and all-*trans* retinoic acid as the cytotoxic agents. Currently, we are investigating more potent agents targeting nuclear receptors and structural proteins. The presentation will highlight various strategies and recent progress towards improved systems, including chemical synthesis, enzyme activity and cytotoxicity.

MEDI 21

Small-molecule and peptide inhibitors of the toll-like receptors

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The protein-protein and protein-RNA interfaces have been regarded as “undruggable” despite their importance in many biological processes. The toll-like receptors provide exciting targets for a number of infectious diseases, pain management, and cancers. Our previous work showed that a rationally designed peptide can disrupt the TLR4–MD2 association, thereby blocking TLR4 signaling. Aiming to identify more drug-like, small molecule inhibitors of these TLRs, we developed a novel in silico screening methodology incorporating Molecular Mechanics (MM)/implicit solvent methods to evaluate binding free energies and applied this technology to the identification of inhibitors of the TLR4/MD-2 interaction. In silico and cellular assay results demonstrated that the identified compounds selectively block TLR4 activation in live cells. Animal model tests showed that these compounds could potentiate morphine-induced analgesia in vivo, presumably by attenuating the opioid-induced TLR4 activation. To demonstrate the general applicability of this methodology, we further developed a series of small-molecule probes that were shown to be competitive inhibitors of dsRNA binding to TLR3 with high affinity and specificity. In a multitude of assays, the optimized small molecule inhibitor was profiled as a potent antagonist to TLR3 signaling and also repressed the expression of downstream signaling pathways mediated by the TLR3/dsRNA complex, including TNF- α and IL-1 β .

MEDI 22

Discovery of small molecule inhibitors of the vitamin D receptor-coregulator interactions as transcriptional regulators for the 24-hydroxylase gene CYP24A1

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The development of new anti-cancer therapies based on vitamin D analogs have been complicated by the fact that these compounds have a high risk of causing hypercalcemia and hypercalciurea. Vitamin D analogs, such as the endogenous vitamin

D analog, 1,25-dihydroxy vitamin D₃ (1,25-(OH)₂D₃), bind to the vitamin D receptor (VDR), which in turn regulates genes responsible for cell differentiation, proliferation, and calcium homeostasis. One of the most important genes regulated by VDR is the 24-hydroxylase gene (CYP24A1), which is over-expressed in many cancers and regulates 1,25-(OH)₂D₃ levels through catabolism. Herein, we describe the identification of novel transcriptional inhibitors of CYP24A1 using high throughput screening. These molecules disrupt the interactions between VDR and coregulator proteins, which are essential for the VDR-mediated expression of CYP24A1. Our hypotheses is that down-regulation of CYP24A1 in the presence of these compounds will locally elevate 1,25-(OH)₂D₃ levels inducing anti-proliferation and differentiation of cancer cells.

MEDI 23

Modular synthesis and biological evaluation of novel estrogen receptor ligands based on a 7-thia-bicyclo[2.2.1]hept-2-ene-7-oxide or 7-oxabicyclo[2.2.1]hept-5-ene skeleton

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The estrogen receptors (ERs), members of the family of nuclear receptors, have emerged as attractive pharmaceutical targets for therapeutic intervention in a wide variety of diseases, including osteoporosis and breast cancer. Our particular interest is to synthesize a series of SERMs possessing a more three-dimensional topology central hydrophobic core. This design strategy was based on structural studies of the ligand binding pockets of both ER α and ER β that reveal substantial unoccupied space above and below the mean plane of the endogenous ligand, estradiol (E₂). By incorporating a hydrophobic bicyclic unit as the core structure of new ligands, we hoped to exploit this unfilled space in the ER binding pocket and thereby, potentially, to enhance the potency (e.g., the binding affinity, selectivity etc). We describe our effects on the development of novel ER ligands based on an inherently three-dimensional 7-thia-bicyclo[2.2.1]hept-2-ene-7-oxide or 7-oxabicyclo[2.2.1]hept-5-ene core structure. Most of these compounds were conveniently synthesized by a Diels-Alder reaction of various 3,4-diarylthiophene or furans with a variety of dienophiles under mild conditions. Some of these ligands have unexpected biological selectivities that could be medically important.

MEDI 24

Small molecule allosteric regulators of coagulation

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A central paradigm of regulating clotting has revolved around targeting the active site of one or more enzymes of the coagulation cascade. Thousands of molecules have been studied as active site inhibitors and a couple have reached the clinic. Yet, antithrombotic therapy continues to suffer from high risk for bleeding and adverse reactions. We propose a novel strategy for new line of coagulation regulation that promises to offer higher selectivity and regulation capability. Our strategy revolves around synthetic, small molecule-based allosteric regulation of thrombin, factor Xa and factor XIa. A small library of approximately 30 molecules was designed based on our macromolecular leads called sulfated low molecular weight lignins. The small molecules were synthesized in less than 10 steps were found to potently inhibit thrombin, factor Xa and factor XIa. The inhibition arises primarily from an allosteric disruption of enzymatic catalytic apparatus. Competitive inhibition studies show that the designed small molecules interact with exosite II-like domain of these enzymes. Studies using A549 lung and HepG2 liver cell lines show no toxicity at concentrations as high as 50 mg/L of the most active molecules. The novel molecular mechanism of action and the novel structural scaffold of these anticoagulants suggest a strong possibility for discovering radically new anticoagulants.

MEDI 25

Computational design development of prolyl oligopeptidase inhibitors

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Prolyl oligopeptidase (POP) is an enzyme implicated in a number of neurodegenerative diseases and neurological disorders. More specifically, it has been identified as a potential therapeutic target in the treatment of Alzheimer's disease. Through the use of our recently developed computational tools for drug discovery (Forecaster platform), covalent and non covalent POP inhibitors were identified and/or designed. Following this design stage, synthesis, and biological evaluation were carried out and were compared to our predictions. Some of the computational tools will first be presented in the context of POP inhibition followed by development of polycyclic chiral inhibitors which required the development of synthetic methodologies and strategies.

MEDI 26

Discovery of a dual CCR2 / CCR5 antagonist with a superior cardiovascular profile for the treatment of autoimmune diseases

Robert O Hughes¹, *robert.o.hughes@pfizer.com*; **D Joseph Rogier**¹; **Rajesh Devraj**¹; **Chu-Biao Xue**²; **Ganfeng Cao**²; **Steven R Turner**¹; **Philip A Morton**¹; **Kelly Keys**¹; **Maryanne Covington**²; **Brian R Bond**¹; **Ying Yu**¹; **Holly Meade**¹; **William F Hood**¹; **Steve Roeberds**¹; **Robert Newton**²; **Brian Metcalfe**². (1) Pfizer Research and Development, Cambridge MA 02451, United States (2) Incyte Corporation, Willmington MA 19880, United States

Chemokines are chemotactic cytokines which are critical for the regulation of cellular trafficking. The chemoattractive activity of the chemokines is mediated through binding to G-protein coupled receptors. Chemokine-receptor binding initiates a cascade of intracellular signalling events mediated by receptor-associated heterotrimeric G proteins, culminating in alterations in the cytoskeleton associated with directed cell migration. Leukocyte trafficking and survival contributes importantly to chronic inflammatory states such as Rheumatoid Arthritis (RA), atherosclerosis, multiple sclerosis (MS) and diabetic nephropathy. The C-C class of chemokine receptors expressed on a subset of leukocytes responsible for both innate and adaptive immunity, particularly CCR1, CCR2, and CCR5, are promising and tractable targets for development of new pharmacological inhibitors of inflammation and autoimmunity. As these chemokine receptors are expressed on a subset of cells responsible for both innate and adaptive immunity, we and others have attempted to develop small molecule antagonists of these members of the C-C chemokine receptor family. Attractive as these targets are, the development of small molecule antagonists has been hampered by the challenging physical property space required to achieve potency and cardiovascular (CV) safety concerns. In this presentation we will disclose some of our findings towards the development of novel orally bioavailable, potent and safe dual inhibitors of CCR2 and CCR5. We describe key preclinical data that led to optimal compound selection. Three generations of clinical candidates will be described.

MEDI 27

PF-4958242: A novel AMPA positive allosteric modulator (PAM) for the treatment of cognitive deficits associated with schizophrenia

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The amino acid neurotransmitter glutamate (Glu) mediates virtually all excitatory neurotransmissions in the mammalian brain and AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors mediate the majority of these neurotransmissions and are essential in a broad range of physiological processes. Glutamate dysregulation/NMDA hypofunction are hypothesized to be key pathologies of schizophrenia and potentiating or modulating AMPA receptors can enhance Glu signaling, improve performance in preclinical models of cognition and improve long term potentiation. The medicinal chemistry strategy along with the preclinical pharmacology, pharmacokinetics and safety data that led to the discovery of PF-4958242, a novel AMPA positive allosteric modulator will be described. PF-4958242 is currently in Ph 1 clinical trials and the single dose escalation human PK data will be disclosed. Taken together, this compound provides an exciting opportunity to treat the cognitive deficits associated with schizophrenia.

MEDI 28

Discovery of TAK-960: An orally available small molecule inhibitor of Polo-Like Kinase 1 (PLK1)

Zhe Nie¹, zhe.nie@takedasd.com; Victoria Feher^{1, 2}; Srinivasa R Natala¹; Christopher McBride¹; Andre Kiryanov¹; Benjamin Jones¹; Betty Lam¹; Yan Liu^{1, 3}; Stephen Kaldor^{1, 4}; Jeffrey Stafford^{1, 5}; Kouki Hikami⁶; Noriko Uchiyama⁶; Tomohiro Kawamoto⁶; Yuichi Hikichi⁶; Lilly Zhang¹; David Hosfield^{1, 7}; Robert Skene¹; Hua Zou¹; Sheldon Cao^{1, 8}; Takashi Ichikawa^{1, 6}. (1) Takeda San Diego, United States (2) UC Irvine, United States (3) University of Florida, United States (4) Kaldor Consulting, United States (5) Quanticell Pharma Inc., United States (6) Takeda Pharmaceutical Company, Ltd., Japan (7) Affinity Pharmaceuticals, United States (8) Cerep Ltd., United States

This oral presentation will focus on the discovery of TAK-960, an orally available, potent and selective PLK1 inhibitor currently in a Phase I clinical trial in patients with advanced non-hematologic malignances. PLK1 inhibition is an attractive approach for the treatment of proliferative diseases, for PLK1 plays a key role in the regulation of mitotic progression and the over-expression of PLK1 is associated with poor prognosis and survival rates in a number of human cancers. Using structure based drug design we identified and optimized a novel series of pyrimidodiazepinone PLK1 inhibitors resulting in the selection of development candidate TAK-960. The discovery of TAK-960 provides an interesting example of how the addition of fluorine atoms during optimization significantly alters the attributes of the leads series. We will show the beneficial influence of adding fluorine atoms on dissociation kinetics of the ligands upon binding to PLK1, MDR1 transporter affinity and oral bioavailability.

MEDI 29

Discovery of GS-9256: A novel phosphinate HCV NS3 protease inhibitor

Christopher Sheng¹, csheng@gilead.com; Mike Clarke¹; Mingzhe Ji¹; Hyungjung Pyun¹; Qiaoyin Wu¹; Ruby Cai¹; Kleem Chaudhary¹; Jianying Wang¹; Chin Tay²; Xiaowu Chen³; Todd Appleby³; Roshly Pakdaman⁴; Chris Yang⁴; Huiling Yang⁵; Margaret Robinson⁵; Ruth Wang⁵; Edward Doerffler¹; Xiaohong Liu⁵; Ona Barauskas⁵; Brian Schultz⁵; Bill Delaney⁵; Choung Kim¹. (1) Dept. of medicinal chemistry, Gilead Sciences Inc, Foster City CA 94404, United States (2) Dept of toxicology, Gilead Sciences Inc, United States (3) Dept of structural chemistry, Gilead Sciences Inc, United States (4) DMPK, Gilead Sciences Inc, United States (5) Dept of biology, Gilead Sciences Inc, United States

GS-9256 is a specific inhibitor of HCV NS3 protease and is currently in phase 2 development for the treatment of genotype 1 (GT1) HCV infection. GS-9256 demonstrated potent and selective inhibition of NS3 protease in biochemical assays (K_i = 90 pM for GT1 NS3 with >10,000-fold selectivity over all tested mammalian proteases). In multiple GT1a and 1b replicon cell lines, GS-9256 had median EC_{50} values of 30 nM and 99 nM, respectively. CC_{50} values ranged between 19,000 – 45,000

nM. This presentation will describe detailed SAR and pharmacokinetic optimizations leading to the discovery of GS-9256.

MEDI 30

Discovery of a potent and selective γ -secretase inhibitor for the treatment of Alzheimer's disease

Wen-Lian Wu¹, wen-lian.wu@merck.com; Theodros Asberom¹; Thomas Bara¹; Chad Bennett¹; Duane Burnett¹; Mary Ann Caplen¹; John Clader¹; David Cole¹; Michael Czarniecki¹; Martin Domalski¹; William J Greenlee¹; Hubert Josien¹; Chad Knutson¹; Hongmei Li¹; Mark McBriar¹; Troy McCracken¹; Brian McKittrick¹; Dmitri Pissarnitski¹; Li Qiang¹; Murali Rajagopalan¹; Thavalakulamgar K Sasikumar¹; Jing Su¹; Haiqun Tang¹; Monica Vicarel¹; Ruo Xu¹; Zhiqiang Zhao¹; Mary Cohen-Williams²; Robert Del Vecchio²; Lynn Hyde²; Prescott Leach²; Julie Lee²; Eric Parker²; Lixin Song²; Giuseppe Terracina²; Lili Zhang²; Qi Zhang²; Shiyang Chen³; Inhou Chu³; Xiaoming Cui³; James Jean³; Amin A Nomeir³; Tony Soares³; Ann Thomas³; Greg Tucker³; Xiaoying Xu³; Qiao Zhou³. (1) Department of Medicinal Chemistry, Merck Research Laboratory, Kenilworth NJ 07033, United States (2) Department of In Vitro and in Vivo Biology, Merck Research Laboratory, Kenilworth NJ 07033, United States (3) Department of Drug Metabolism & Pharmacokinetics, Merck Research Laboratory, Kenilworth NJ 07033, United States

Alzheimer's disease (AD) is a neurodegenerative disorder manifested by cognitive impairment, behavioral disturbances, speech difficulties, and deterioration of many other activities of daily life. Two major pathological hallmarks of AD are intracellular neurofibrillary tangles and extracellular amyloid plaques. The latter is mainly comprised of aggregated forms of the 40-42 residue amyloid β -peptides ($A\beta$), which are produced by sequential cleavage of the amyloid precursor protein (APP) by BACE and γ -secretase. Reduction of $A\beta$ by inhibition of γ -secretase represents an attractive strategy to combat Alzheimer's disease. In addition to APP, γ -secretase has many other substrates, notably Notch. Inhibition of Notch processing is responsible for many of the mechanism-based side effects associated with γ -secretase inhibition. It is imperative to balance the therapeutic efficacy and the risk of mechanism-based toxicity. Starting from a known sulfone-based γ -secretase inhibitor (GSI), conformational restriction led to a novel series of tricyclic analogs. Further optimization of the tricyclic core and the side chain culminated in the discovery of a clinical candidate, which demonstrated excellent *in vitro* and *in vivo* efficacy in several animal models with a high therapeutic window.

MEDI 31

Design and synthesis of novel macrocyclic structures as potent Hsp90 inhibitors

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We wish to disclose a series of macrocyclic lactones and lactams some of which have been found to be highly potent at inhibiting Hsp90 in an enzyme and cell-based assays. The lactones and lactams were accessed by novel synthetic methods which allowed their preparation in good yields. Based on potency and physical properties we selected analogs for X-ray crystallography as well as in vivo tumor exposure and biomarker studies.

MEDI 32

Synthesis and evaluation of pyrazole analogs as antimitotic agents

Yuuki Hirata¹, yuuki.hirata@kyowa-kirin.co.jp; Tomoyuki Nakazato¹; Yusuke Yamada¹; Toshikazu Saitoh¹; Kazuhiko Kato¹; Junichiro Yamamoto¹; Kimihisa Ueno¹; Yoshisuke Nakasato¹; Asae Igarashi²; Ryuichiro Naka²; Tetsuo Yoshida³; Shinji Nara¹. (1) Department of Medicinal Chemistry Research Laboratories, Kyowa Hakko Kirin Co.,Ltd., 1188 Shimotogari, Nagaizumi-cho Sunto-gun, Shizuoka 411-8731, Japan (2) Department of Drug Discovery Research Laboratories, Kyowa Hakko Kirin Co.,Ltd., Japan (3) Department of Innovative Drug Research Laboratories, Kyowa Hakko Kirin Co.,Ltd, Japan

Compound **1** was found as an antimitotic agent. Compound **1** induced mitotic arrest and cell growth inhibition in tumor cells, suggesting that compound **1** could be a potential candidate as an anticancer agent. The derivative analogues of the compound **1** were synthesized using S_NAr-type or copper-catalyzed reaction between pyrazoles **2** and 2-halothiazoles **3**. Several analogues exhibited significant improvement in the antiproliferative activity against HeLa cells. Synthetic studies and SAR of pyrazoles and quinolones will be presented.

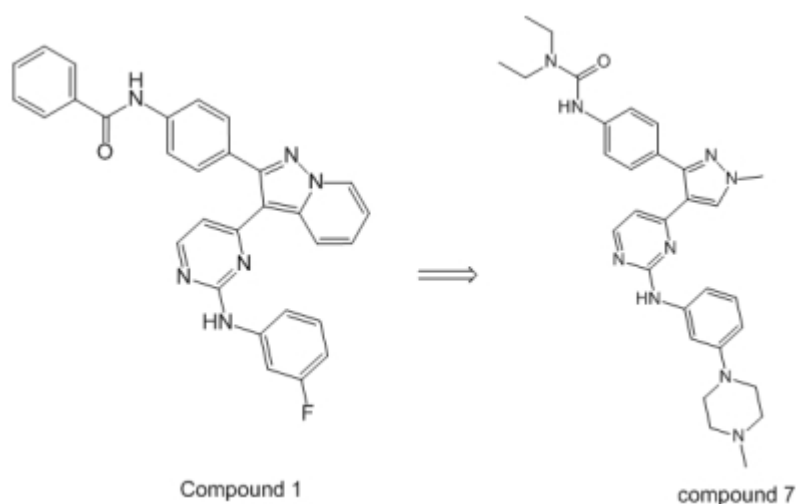


MEDI 33

N-alkylated diaryl pyrazoles: Selective Aurora kinase inhibitors

Jeffrey M. Ralph, Jeffrey.m.ralph@gsk.com; Yanhong Feng; Thomas H Faitg; Domingos J Silva; Jerry L Adams; Mary Ann Hardwicke; Jamin Wang; Catherine Oleykowski; Melody Diamond; David Sutton; Leo Faucette; Ramona Plant. Oncology R&D, Protein Dynamics DPU, GlaxoSmithKline, 1250 S. Collegeville Rd, Collegeville PA 19426, United States

A series of N-alkylated diaryl pyrazoles has been prepared as inhibitors of Aurora B. Originally pursued as ErbB+ kinase inhibitors, pyrazolopyridines such as compound 1 were identified as early leads for the Aurora effort. These compounds displayed good activity against Aurora B in enzymatic and cellular assays. However, the series suffered from poor developability, which we attributed to high molecular weight and clogP. In an effort to identify more developable Aurora inhibitors, we have investigated the corresponding pyrazoles, derived from the pyrazolopyridines by removal of the central phenyl ring. The pyrazoles proved to be excellent Aurora inhibitors, with potent enzymatic and cellular activities, good kinase selectivity and improved developability properties.

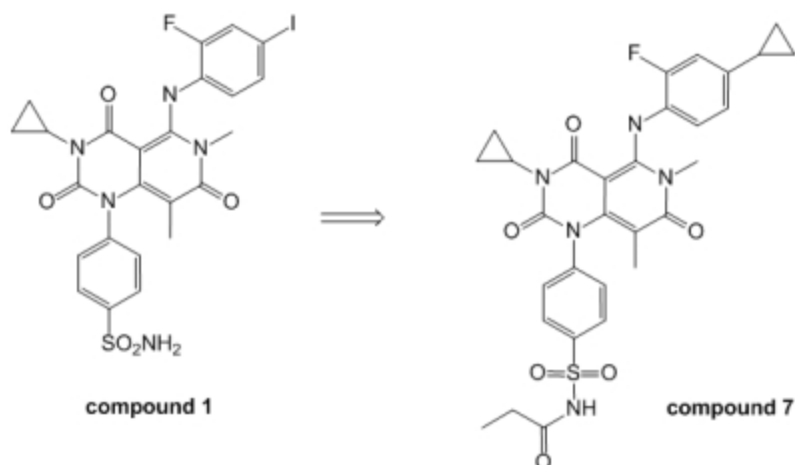


MEDI 34

Evaluation of N-acyl sulfonamide prodrug inhibitors of MEK kinase

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A series of novel N-acylsulfonamide prodrugs were evaluated and profiled as inhibitors of MEK kinase. Our pursuit of MEK inhibitors led us to compound 1, which displayed highly potent and selective inhibition of MEK enzymatic and cellular activities. However, compound 1 had poor solubility and no oral exposure in rats. Using a prodrug approach, solubility and pharmacokinetic parameters of a series of MEK inhibitors were improved, culminating in the discovery of the propionyl sulphonamide 7. Optimization led to the discovery of compound 7, which showed improved solubility and PK. This poster describes the SAR leading to compound 7 and the multi-species in vitro and in vivo PK to support compound 7 as a potential candidate.



MEDI 35

Exploitation of multitarget prostate cancer clinical candidate VN/124-1 (TOK-001) to develop a novel class of androgen receptor down regulating agents for prostate cancer therapy

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The androgen receptor (AR) is a critical mediator of prostate cancer (PC) proliferation at virtually all stages of PC, including the dreaded castration-resistant stage. Selective AR down-regulators (SARDs) reduce AR protein levels as well as block AR activity and therefore are promising agents for the treatment of PC. Our clinical candidate novel **VN/124-1 (TOK-001)** is a potent CYP17 inhibitor/antiandrogen with modest AR down-regulating activity ($EC_{50} \sim 10 \mu M$). In the present study we used **VN/124-1** to conduct lead optimization to develop a novel class of AR down-regulating agents. A series of new compounds were designed, synthesized and evaluated for their abilities to suppress AR expression in LNCaP cells and inhibition of LNCaP cell viability by Western blot analysis and MTT assay, respectively. Our design strategy involved systematic modification of rings A, B or D; and modifications at C-3, C-16 and C-17 of our lead **VN/124-1**, resulted in novel potent anti-PC agents.

MEDI 36

Library of chimera of novoniocin and silybin manifest antiproliferative activity through Hsp90 inhibition

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Hsp90 is a promising therapeutic target for cancer and neurodegenerative diseases. The potential therapeutic benefits associated with Hsp90 modulation highlight the importance of identifying novel Hsp90 modulators. Novobiocin and silybin were identified as Hsp90 inhibitors and SAR studies revealed essential structural features for their Hsp90 modulation. A library of chimerical compounds incorporated these structural features were designed and synthesized, their biological activities were evaluated in multiple cancer cell lines.

MEDI 37

Potent and selective cyclic sulfones as mTOR selective inhibitors

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mTOR is a protein kinase and member of the phosphoinositide-3-kinase-related kinase (PIKK) family. Genomic aberrations in PI3K pathway are the 2nd most frequent in human cancers. The catalytic domain of mTOR comprises at least two functional complexes, mTORC1 (raptor) and mTORC2 (rictor), which play critical roles in cellular signaling, growth and survival, metabolism, and protein synthesis. Rapamycin and its analogs (Raplogs) target mTORC1 only and they are known to only give modest clinical efficacy. We are hoping that mTOR kinase inhibitors which not only inhibit mTORC1 but also mTORC2 as well may yield a more efficacious anti-cancer agent. A series of mTORC1 and 2 selective inhibitors with a cyclic sulfone scaffold are described showing excellent biochemical potencies, selectivities over PI3Ka and other broad-panel kinases. The SAR of this series compounds will be discussed

MEDI 38

Discovery of TAK-960 part II: Development and in vivo characterization of 7,7-difluoro-pyrimidodiazepinone derivatives as potent inhibitors of Polo-like Kinase 1 (PLK1)

Christopher McBride¹, *chris.mcbride@takedasd.com*; **Zhe Nie**¹; **Victoria Feher**^{1, 2}; **Srinivasa Nataka**¹; **Andre Kiryanov**¹; **Benjamin Jones**¹; **Betty Lam**¹; **Yan Liu**^{1, 3}; **Stephen Kaldor**^{1, 4}; **Jeffrey Stafford**^{1, 5}; **Kouki Hikami**⁶; **Noriko Uchiyama**⁶; **Tomohiro Kawamoto**⁶; **Yuichi Hikichi**⁶; **Lilly Zhang**¹; **David Hosfield**^{1, 7}; **Robert Skene**¹; **Hua Zou**¹; **Sheldon Cao**^{1, 8}; **Takashi Ichikawa**^{1, 6}. (1) Takeda San Diego, United States (2) UC Irvine, United States (3) University of Florida, United States (4) Kaldor Consulting, United States (5) Quanticell Pharma, Inc, United States (6) Takeda Pharmaceutical Company, Ltd., Japan (7) Affinity Pharmaceuticals, United States (8) Cerep Ltd., United States

This poster describes the identification of the clinical candidate TAK-960, an orally available and highly selective small molecule Polo-like Kinase 1 (PLK1) inhibitor currently in a Phase I study in patients with advanced non-hematologic malignancies. PLK1 inhibition is an attractive approach for the treatment of proliferative diseases based on its key role in the regulation of mitotic progression. The over-expression of PLK1 is associated with poor prognosis and survival rates in a number of human cancers. In Part I of this presentation, we discussed the structure based design of a 7,7-difluoro-8,9-dihydro-5*H*-pyrimido[4,5-*b*][1,4]diazepin-6(7*H*)-one lead scaffold which binds PLK1 in an ATP competitive manner and exhibits slow dissociation kinetics. This part of the presentation will describe amendments to the C², N⁵, and N⁹ positions of the core and the resulting *in vitro* properties (enzymatic binding, cellular activity, DMPK). Herein, we also share some results from the pharmacokinetic, pharmacodynamic and efficacy studies which led to the identification of TAK-960. This work provides a noteworthy example of how the addition of fluorine atoms during optimization significantly alters the attributes of the lead series. TAK-960 is active against a broad spectrum of cancer cell lines including MDR1 expressing cell lines.

MEDI 39

Discovery of TAK-960 Part I: Design and synthesis of 7,7-difluoro-pyrimidodiazepinone derivatives as potent inhibitors of Polo-like Kinase 1 (PLK1)

Srinivasa Reddy Natala¹, snatala@takedasd.com; Zhe Nie¹; Victoria Feher^{1, 2}; Christopher McBride¹; Andre Kiryanov¹; Benjamin Jones¹; Betty Lam¹; Yan Liu^{1, 3}; Stephen Kaldor^{1, 4}; Jeffrey Stafford^{1, 5}; Kouki Hikami⁶; Noriko Uchiyama⁶; Tomohiro Kawamoto⁶; Yuichi Hikichi⁶; Lilly Zhang¹; David Hosfield^{1, 7}; Robert Skene¹; Hua Zou¹; Sheldon Cao^{1, 8}; Takashi Ichikawa^{1, 6}. (1) Takeda San Diego, United States (2) Current: UC Irvine, United States (3) Current: Moffitt Cancer Center, United States (4) Current: Kaldor Consulting, United States (5) Current: Quanticell Pharma, Inc, United States (6) Takeda Pharmaceutical Company, Ltd., Japan (7) Current: Affinity Pharmaceuticals, United States (8) Current: Cerep Ltd, United States

Polo-like Kinase 1 (PLK1) has recently emerged as an attractive drug target for treating proliferative disorders such as cancer. PLK1 is overexpressed in variety of human cancers and is associated with poor prognosis and survival rates. PLK1 plays a critical role in the cell cycle, controlling entry into and progression through mitosis at multiple stages. Inhibition of PLK1 function causes G2/M cell cycle arrest and tumor cell apoptosis resulting in tumor growth suppression, which has been observed in both animal models and clinical evidence from humans. In comparison to marketed antimicrotubule drugs (i.e. Taxanes and Vincas), inhibitors of PLK1 are expected to be more selective for mitosis and mitigate side effects such as neuropathy. In this presentation, we will discuss the structure based design of an 8,9-dihydro-5*H*-pyrimido[4,5-*b*][1,4]diazepin-6(7*H*)-one core and the structure activity relationship studies of its C7-position. This investigation led us to the identification of novel and potent 7,7-difluoro-pyrimidodiazepinone derivatives as PLK1 inhibitors. Analysis of co-crystal structures of this series demonstrates that appropriate C7 substitutions interact

favorably with “roof pocket” and adjacent water molecules which were believed to contribute to their improved enzyme potency, efficacy and slow dissociation kinetics. Further lead optimization of this series (Part II), led to the identification of a novel orally available small molecule PLK1 inhibitor TAK-960, which is currently in Phase-I clinical trial.

MEDI 40

Design and synthesis of novel HER2/EGFR dual inhibitors: Discovery of TAK-285 bearing a pyrrolo[3,2-*d*]pyrimidine scaffold

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Pyrrolo[3,2-*d*]pyrimidine derivatives capable of fitting into the ATP binding site of the HER2/EGFR protein were designed and synthesized. The clinical candidate, TAK-285, potently inhibited HER2 and EGFR with IC₅₀ values of 17 and 23 nM, respectively, indicating selective inhibition of the HER family kinases. TAK-285 also inhibited the growth of the HER2-overexpressing human breast cancer cell line BT474 (GI₅₀ 17 nM). Furthermore, reflecting its good oral bioavailability, TAK-285 exhibited potent, dose-dependent efficacy in rats and inhibited the growth of HER2-overexpressing 4-1ST tumors with T/C of 38% and 14% at 6.25 and 12.5 mg/kg and, notably, tumor regression with T/C of -12% and -16% at 25 and 50 mg/kg. The first X-ray co-crystal structures of TAK-285 with HER2 and EGFR demonstrated TAK-285 interaction with the expected residues in their respective ATP pockets. Therefore, TAK-285 appears to be a promising candidate for clinical development as a novel HER2/EGFR dual kinase inhibitor.

MEDI 41

Molecular dynamics simulation studies of recognition of anticancer drug-induced DNA damage by repair proteins

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Platinum-based chemotherapeutic drugs, such as cisplatin, work by covalently binding to DNA, inducing severe local structural changes. Numerous proteins, including DNA repair and tumor-suppressor proteins, recognize these structural changes induced by the drug-DNA adducts. Some of these protein-DNA interactions lead to arrest of the cell

cycle and apoptosis of the cancer cells, which leads to high cure rates for certain cancers. However, some protein-DNA interactions lead to repair of the drug-DNA adduct and resistance to the drug. In order to circumvent and develop better drug, one needs to understand the molecular-mechanism underlying differential recognition of the various drug-DNA adducts. We use atomistic molecular dynamics simulations to probe the thermodynamic and structural differences in protein-drug-DNA complexes with the goal of engineering new drugs with desirable protein interactions.

MEDI 42

DNA methyltransferase inhibitors: Homology modeling, docking, and structure-based pharmacophore

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DNA methylation is a covalent chemical modification of DNA catalyzed by DNA methyltransferases (DNMTs) and plays a crucial role in epigenetic modifications. Inhibition of DNMT is a promising strategy for the treatment of cancer and other diseases. To understand the interaction of known inhibitors with DNMT1, we performed docking studies of DNMT1 inhibitors with a homology model of the catalytic domain of human DNMT1. The docking models allowed the identification of key molecular interactions between the inhibitors and the binding pocket. We also report a structure-based pharmacophore model that was derived from the optimized docked conformations of the inhibitors [1]. The common pharmacophore features are in agreement with the hypothetical binding profile proposed by docking studies. The results of this work will be valuable for the structure-based design and virtual screening for novel inhibitors targeting DNMT1 [2]. [1] Yoo, J.; Medina-Franco, J. L. J. Comp.-Aided Mol. Des., submitted. [2] Medina-Franco, J. L.; Caulfield, T. Drug Discovery Today, (2011) in press. PMID: 21315180.

MEDI 43

Identification of novel and potent ALK inhibitor CH5424802

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Anaplastic lymphoma kinase (ALK) is a tyrosine kinase that is constitutively activated in some cancers, due to gene alterations such as chromosomal translocation, amplification, or point mutation. We discovered a compound with a unique tetracyclic structure showing inhibitory activity against ALK from our corporate library. Our

chemical modification of the scaffold enabled us to select CH5424802 as a clinical candidate. CH5424802 has a preferable PK profile and good oral bioavailability in rats and monkeys, and showed preferential antitumor activity against cancers with gene alterations of ALK, such as non-small cell lung cancer (NSCLC) cells expressing EML4-ALK fusion both *in vitro* and *in vivo*. CH5424802 also inhibited ALK L1196M, which corresponds to the gatekeeper mutation conferring common resistance to kinase inhibitors. CH5424802 is currently being investigated in Phase I/II clinical trials for patients with ALK-positive NSCLC. Our poster presentation will also show the synthesis of the tetracyclic derivatives and the modification strategy to improve kinase selectivity and metabolic stability as well as ALK inhibition potency.

MEDI 44

Design and synthesis of novel linkable proteasome inhibitors and their folate conjugates

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In this poster we present our results related to the design and synthesis of novel proteasome inhibitors and their conjugates with folic acid (FA). *In vivo* FA will serve as a high affinity ligand for the folate receptor – a protein, highly expressed on the outer layer of cellular membranes in a variety of cancer types. Consequently, such approach might prove to be useful for targeted treatment of solid tumors thus minimizing side effects, associated with the therapeutic applications of non-targeted cytotoxic agents. In the molecular drug design we focused our attention on boronic-acid-based proteasome inhibitors. In their chemical structures we placed several linkable functional groups serving as regioselective site of conjugation. All conjugates were synthesized using a proprietary protocol and involving incorporation of two additional molecular modules in the construct: a carbohydrate-based, negatively charged spacer unit, and a bio-releasable disulfide-based linker system.

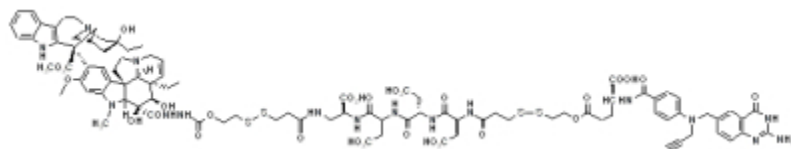
MEDI 45

Folate receptor binding conjugates of antifolate

Fei You, *Fei_You@Endocyte.com*; **Iontcho R. Vlahov**; **Christopher P. Leamon**. Endocyte, Inc., West Lafayette IN 47906, United States

Antifolates are used in cancer chemotherapy by interfering DNA and RNA synthesis of cancer cells. Some antifolates have high binding affinity to folate receptor (FR). FR is frequently over-expressed in some of the most prevalent tumors. FR-binding antifolates can be used as ligands for FR-targeted delivery of therapeutic agents. To demonstrate the dual roles of antifolates as ligands and therapeutic agents, we reported here an

improved synthesis of antifolate CB3717 and its conjugates of cytotoxic molecules. A hydrophilic spacer unit and two biologically releasable disulfide-based linker systems were used to construct the conjugates. These conjugates showed high relative affinity for FR and excellent anti-tumor activities.



MEDI 46

Efficient total synthesis of Tubulysin B

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Tubulysins are natural products isolated from myxobacterial species. As cytoskeleton interacting agents, tubulysins are mitotic poisons and are extremely potent cytotoxins, thus exceeding the cell growth inhibition of any clinically relevant traditional chemotherapeutic. Structurally, tubulysins are closely related linear tetrapeptides comprised of unusual and/or hydrophobic amino acid segments. The isolation of a single natural tubulysin from culture extracts requires multistep chromatography and provides only limited quantities. Several total syntheses of natural tubulysins and some structurally simplified analogues have been reported, but their application is limited to small lab scale. Among the multiple challenging synthetic and stereochemical issues, most striking is the generation of the labile *N,O*-diacyl *N,O*-acetal. In this poster we present an efficient yet simplified synthesis of tubulysin B. The optimized synthetic protocol relies on chemical as well as enzymatic steps and is readily scalable to meaningful quantities.

MEDI 47

Property guided design of a brain penetrant PI3K inhibitor

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The well documented deregulation of the PI3K/AKT/mTOR pathway in numerous tumor types has established a significant desire for PI3K inhibitors with drug-like properties. Furthermore, activation of the PI3K pathway is observed in the majority of all glioblastomas. This highlights the need for brain penetrant PI3K inhibitors. This poster will discuss how we used property-guided design to achieve significant brain penetration with PI3K inhibitors.

MEDI 48

Design, synthesis and biological evaluation of novel, conformationally restricted, water soluble, substituted pyrrolo[3,2-*d*]pyrimidines as antitubulin antitumor agents

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Despite the unprecedented success of microtubule disrupting agents in cancer chemotherapy, multidrug resistance (MDR) is a major limitation of cancer chemotherapy, and MDR tumors are usually resistant to tubulin-binding drugs. Our efforts in the design of multiple RTK-inhibitors to elucidate the plausible binding modes of our compounds led to the discovery of highly potent antimitotic antitumor agents that bind to the colchicine-binding site of tubulin and also overcome clinically relevant mechanisms of drug resistance: P-glycoprotein and β III-Tubulin mediated resistance. Conformationally restricted pyrrolo[3,2-*d*]pyrimidine analogs of the lead compounds were designed and synthesized. These compounds inhibited microtubule polymerization and had GI₅₀'s which were two-digit nanomolar against tumor cells in the NCI 60 human tumor cell line anticancer drug screen. The design, synthesis and biological activities of these analogs will be presented.

MEDI 49

Synthesis and biological evaluation of some 16b-azolyl-3b-amino-5a-androstane derivatives as potential anticancer agents

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Nitrogen containing steroids have the ability to regulate a variety of biological processes and thus are potential drug candidates for the treatment of a large number of diseases. An increasing numbers of publications had recently reported the anticancer activities of a wide range of natural, semisynthetic and synthetic aminosteroidal compounds. However, to the best of our knowledge, little attention has been given to 16-azolyl-3-amino-androstanes. On the basis of the above details, we synthesized a series of androstane-based aminosteroids to screen their anticancer activity against different cancer cell lines in vitro in order to get more potent anticancer agents. The routes

utilized for the synthesis of our target compounds 16a-g,18a-g,18a-g,19a-g are outlined in Figure1

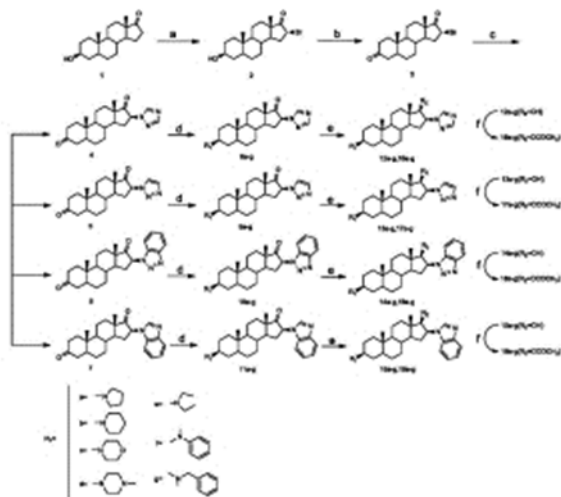


Figure 1. Preparation of target compounds(16a-g,17a-g,18a-g,19a-g). Reagents and Conditions: (a) CuBr_2 , MeOH, 65°C , 12h; (b) Jones Reagent, acetone, 100°C ; (c) appropriate acids, K_2CO_3 , CH_3CN , $65-80^\circ\text{C}$; (d) appropriate amine, NaBH_4/CN , MeOH, 40°C , 24h; (e) NaBH_4 , MeOH, 100°C , 4h; (f) Acetic Anhydride, 4-Dimethylaminopyridine, CH_2Cl_2 , 40°C .

The new compounds were screened for their anticancer activity against the human cancer cell lines SW480,A549,HepG2, HeLa and SiHa in vitro using the MTT assay. The results of the in vitro study showed that a number of compounds have shown IC_{50} values lower than $20\mu\text{M}$ against the five cancer cell lines.

MEDI 50

Indenoisoquinolines: A new class of rexinoids with promising chemopreventive potential

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The retinoid X receptor (RXR) plays an important role in cell differentiation, proliferation, and apoptosis. Activation of the RXR transcriptional activity by synthetic ligands termed rexinoids is a promising chemopreventive strategy. An indenoisoquinoline synthesized in our laboratory, AM-6-36, was found to induce the transcriptional activity of this receptor response-element in a dose-dependent manner, as determined in a luciferase assay, and upregulated the cyclin-dependent kinase inhibitor $\text{p}21^{\text{WAF1/CIP1}}$. This report will detail the synthesis and biological evaluation of the metabolic products of the RXR ligand AM-6-36. In addition, the synthesis and biological evaluation of a series of

analogs will be reported. AM-6-36 and some of its analogs had in vitro potencies greater than the clinically used drug bexarotene. These results provide a foundation for the development of a new class of promising RXR activating ligands.

MEDI 51

Synthesis of [^{11}C]Vandetanib and [^{11}C]chloro-Vandetanib as new potential PET cancer imaging agents for VEGFR

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Vandetanib [*N*-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine], also known as ZD6474, is an antagonist of the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR), and it is tyrosine kinase inhibitor, developed by AstraZeneca as a cancer therapeutic agent. VEGF is the most common and direct acting angiogenic factor in cancer. Vandetanib and its chloro-analog [chloro-Vandetanib, *N*-(4-chloro-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine] displayed relatively low nanomolar IC₅₀ values for VEGF compared to EGF. Carbon-11-labeled Vandetanib and chloro-Vandetanib may serve as new probes for the biomedical imaging technique positron emission tomography (PET), and enable non-invasive monitoring of VEGFR in cancer. Here we report the synthesis of [^{11}C]Vandetanib and [^{11}C]chloro-Vandetanib as new PET cancer imaging agents for VEGFR. Vandetanib and chloro-Vandetanib, and their corresponding *N*- and *O*-desmethylated precursors for radiolabeling were synthesized from 7-(benzyloxy)-4-chloro-6-methoxyquinazoline in 5, 4 and 6 steps with 39% and 41%, 46% and 49%, 7% and 7% overall chemical yields, respectively. The *N*- or *O*-desmethylated precursors were labeled with [^{11}C]CH₃OTf under basic conditions through either *N*- or *O*-[^{11}C]methylation to provide the target tracers [^{11}C]Vandetanib {*N*-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-[^{11}C]methylpiperidin-4-yl)methoxy)quinazolin-4-amine or *N*-(4-bromo-2-fluorophenyl)-6-[^{11}C]methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine} and [^{11}C]chloro-Vandetanib {*N*-(4-chloro-2-fluorophenyl)-6-methoxy-7-((1-[^{11}C]methylpiperidin-4-yl)methoxy)quinazolin-4-amine or *N*-(4-chloro-2-fluorophenyl)-6-[^{11}C]methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine} in 40-50% decay corrected radiochemical yields based on [^{11}C]CO₂, and 370-555 GBq/μmol specific activity at end of bombardment (EOB). The radiolabeling reaction was performed in a home-built automated ^{11}C -radiosynthesis module, and the target tracer was purified by HPLC. In summary, a synthetic route to labeling *N*- and *O*-desmethylated precursors and Vandetanib and chloro-Vandetanib has been described, and a radiosynthesis approach to [^{11}C]Vandetanib and [^{11}C]chloro-Vandetanib via either *N*- or *O*-[^{11}C]methylation has been developed.

MEDI 52

Synthesis and biological evaluation of N^4 -(substitutedphenyl)- N^4 -methyl/desmethyl-9*H*-pyrimido[4,5-*b*]indole-2,4-diamines as antimitotic agents

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Paclitaxel and vinblastine are established antimitotic agents used for the treatment of cancer. However their efficacy is limited by multidrug resistance (MDR). In 2010, we reported *N*-(4-methoxyphenyl)-*N*-2,6-trimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine as a potent cytotoxic agent with microtubule depolymerizing activities. This compound inhibits tubulin polymerization and the binding of [³H]colchicine to tubulin. This agent also circumvents clinically relevant mechanisms of drug resistance. Further analogue design afforded a series of nine N^4 -(substituted phenyl)- N^4 -methyl/desmethyl-9*H*-pyrimido[4,5-*b*]indole-2,4-diamines. The synthesis involved a Fisher indole cyclization of 2-amino-6-hydrazinylpyrimidin-4(3*H*)-one with cyclohexanone, followed by oxidation, chlorination and aniline displacement. One of these compounds displayed low nanomolar inhibition of MDA-MB-435 tumor cells. This agent demonstrated nanomolar GI₅₀ values against 57 of the NCI 60 panel cell lines in the NCI 60 panel and was therefore selected for advancement to hollow fiber assay in vivo screen. The synthesis, and preliminary biological activity of this series will be presented.

MEDI 53

Synthesis and biological evaluation of 5-chloro- N^4 -substituted- N^4 -methyl-9*H*-pyrimido[4,5-*b*]indole-2,4-diamines as antimitotic agents

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Agents that interfere with microtubules including the vinca alkaloids and the taxanes are important antitumor agents. Despite the unprecedented success of these agents in cancer chemotherapy, multidrug resistance is a major limitation. We recently reported *N*-(4-methoxyphenyl)-*N*-2,6-trimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-amine (**1**) as a potent antimitotic tubulin-binding agent. This compound inhibits tubulin polymerization, the binding of [³H]colchicine to tubulin, and circumvents clinically relevant mechanisms of drug resistance. Further analog design from lead compound **1** yielded 5-chloro- N^4 -(4-methoxyphenyl)- N^4 -methyl-9*H*-pyrimido[4,5-*b*]indole-2,4-diamine (**2**). The synthesis of **2** was accomplished by simultaneous displacement of the 4-chloro

group of known *N*-(4,5-dichloro-9*H*-pyrimido[4,5-*b*]indol-2-yl)pivalamide with 4-methoxy-*N*-methylaniline and deprotection. Compound **2** is a potent inhibitor of MDA-MB-435 tumor cells in culture and was selected for in vivo screen in the hollow fiber assay of the NCI Developmental Therapeutics Program. This prompted the design of five novel analogues with variations in the aniline substitution. The synthesis, and preliminary biological activity of **2** and its analogs will be presented.

MEDI 54

Syntheses and antitumor activities on NCI-60 human tumor cell line protocol of *N*-hydroxyethyl-4-aza-didehyropodophyllotoxin derivatives

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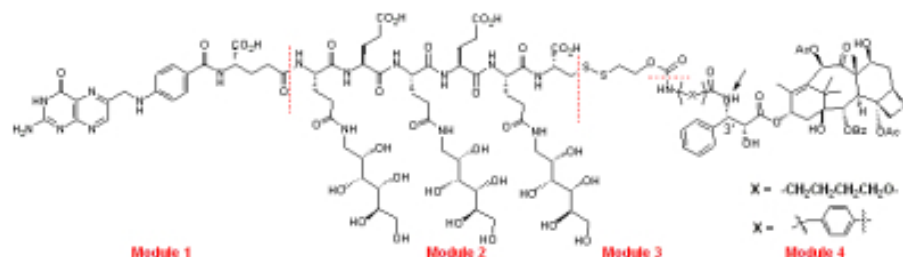
Podophyllotoxin has been known to possess anti-tumor activity and is still considered an important lead for research and development of antineoplastic agents. Derivatives of podophyllotoxin, namely etoposide, etopophos and teniposide have been developed and are currently used in clinic for the treatment of a variety of malignancies. The structural complexity of podophyllotoxin, arising from the presence of four stereogenic carbons in ring C has restricted most of the structural activity relationship (SAR) studied by derivatization of the parent natural product rather than by *de novo* multi-step chemical synthesis. A library of *N*-hydroxy aza-podophyllotoxin derivatives were screened for their antitumor activity using the National Cancer Institute's 60 human tumor cell lines protocol to study their structure activity relationships. This was followed by a screen of in vivo activity using a panel of tumor hollow-grafts implanted in mice consisting of breast (MDA-MB-231), non-small lung (NCI-H23 and NCI-H522), colon (SW-620 and COLO 205), melanoma (UACC-62, MDA-MB-435 and LOXIMVI), ovarian (OVCAR-5 and OVCAR-3) and CNS (U251 and SF-295) cell lines. This is the first report of aza-podophyllotoxins anticancer activity evaluation on such a broad panel of cancer cell lines. The toxicity of all the active compounds was low, while their antiproliferative activity was high, providing a wide therapeutic window for their potential application as anticancer drugs.

MEDI 55

Design and synthesis of novel taxol analogs and thier folate conjugates

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The taxanes are diterpene natural products isolated from the bark of *Taxus brevifolia* and the pacific yew. Taxanes stabilize microtubules, thereby inhibiting the process of cell division. Taxanes are recognized as one of the most important drugs available for treatment of solid tumors. However, there are severe side effects associated with administering any non-targeted drugs. Receptor targeted, releasable, drug conjugates selectively deliver toxic agents into pathologic cells, minimizing toxicity to normal cells. In this poster we report the design and synthesis of novel 3'-amino functionalized semi-synthetic taxanes. Further, these compounds are conjugated *via* proprietary modular approach, comprised of: the ligand folic acid (FA), a highly charged water-soluble carbohydrate-based spacer unit, a self-immolative linker system containing a reducible disulfide bond, and the taxane.

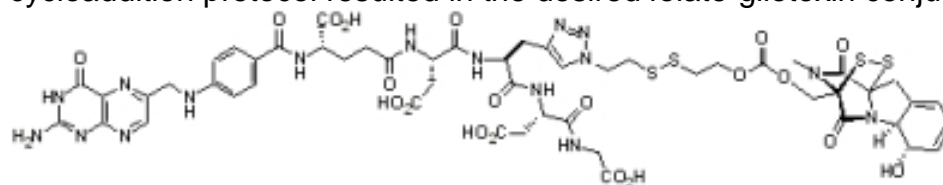


MEDI 56

Synthesis of a releasable folate conjugate of gliotoxin

Paul J. Kleindl, pkleindl@endocyte.com; **Iontcho R. Vlahov**; **Hari K. Santhapuram**; **Christopher P. Leamon**. Endocyte Inc., W. Lafayette Indiana 47906, United States

Gliotoxin, a member of the epipolythiodioxypiperazine (ETP) class of natural mycotoxins, has shown the ability to induce apoptosis (programmed cell death) in a number of cell lines and has also shown anti-inflammatory activity. Unfortunately, systemic toxicities have prevented the advancement of gliotoxin as a therapeutic agent. Synthesis of a releasable, folate conjugate of gliotoxin has the potential to reduce side-effects by targeting only cancer cells and activated macrophages which overexpress the folate receptor (FR). The primary $-OH$ on gliotoxin was regioselectively modified to form an azido-ethyldisulfanyylethyl carbonate adduct. Reaction of this adduct with a propargylglycine containing, water soluble, peptidic, folate spacer following a Huisgen cycloaddition protocol resulted in the desired folate-gliotoxin conjugate.



MEDI 57

Design and synthesis of folate-valinomycin conjugate

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Valinomycin is a dodecadepsipeptide antibiotic that selectively transports potassium ion across biological membranes, causing damage to bacteria cells. It has been reported to display antitumor activities, but its use has been limited due to high toxicity. Selective targeting receptors overexpressed on pathologic cells with ligand-drug conjugates provide an opportunity to reduce toxicity to normal cells. In this poster we present the design of valinomycin conjugates targeting folate receptor (FR) positive pathologic cells. Furthermore we report the total synthesis of a novel valinomycin derivative exploiting solid-support-based macrolactamization as a key reaction step. A phenol group, introduced in the macrocyclic backbone of valinomycin, serves as a tether for attachment of carbohydrate-based hydrophilic spacers via a disulfide-based release system.

MEDI 58

2-Methyl-6-substituted pyrrolo[2,3-d]pyrimidine classical antifolates as selective folate receptor substrates, glycinamide ribonucleotide formyltransferase inhibitors and antitumor agents

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The important role of reduced folates in one-carbon transfer reactions has made folate metabolism an attractive target in cancer chemotherapy for decades. Clinically used antifolates enter cells via folate uptake systems, such as reduced folate carrier (RFC), folate receptors (FRs), and proton-coupled folate transporter (PCFT). Toxicity of clinically used antifolates is due to their lack of selectivity for tumor cells, since these antifolates are transported by RFC which occurs in normal as well as tumor cells. FR is usually not expressed in normal cells. However, FR is expressed in some tumor cells, such as ovarian, breast etc. Thus specific FR targeted agents that also possess cytotoxic activity without transport by RFC circumvent the major toxicities of currently used antifolates that all use RFC for transport. 2-Methyl-6-substituted pyrrolo[2,3-d]pyrimidine antifolates were designed to evaluate the importance of the 2-amino group for transport by RFC, FR, and /or PCFT as well as for inhibition of folate metabolizing enzymes. This report will present the design, synthesis and evaluation of the title compounds.

MEDI 59

Mechanistic studies to determine how using cell-delivered nanoparticles to cause local hyperthermia increases survival in a murine metastatic pancreatic cancer model

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We have previously demonstrated that cell-delivered-nanoparticle-generated (CDNG) hyperthermia can increase survival in a murine metastatic pancreatic cancer model. This system uses tumor homing monocyte/macrophage-like cells (Mo/Ma) to deliver magnetic nanoparticles specifically to tumor tissues. Treating with AMF induces hyperthermia. Here we explore the mechanisms of how CDNG hyperthermia works. A murine model of metastatic pancreatic cancer was created by injecting Pan02 cells intraperitoneally into C57BL/6 mice. Mice were treated on days 5, 9, and 13 with nanoparticle loaded Mo/Ma (or appropriate controls). On days 8, 12, and 16, mice were treated with 30 minutes of alternating magnetic fields to induce hyperthermia. Mice were then euthanatized and tissues were collected and fixed. Sections were made and were examined using immunohistochemistry, western blots, and/or RT-PCR for a variety of hyperthermia markers, immune cell markers and apoptosis markers. These data were then examined to determine what mechanism(s) might be operative in CDNG hyperthermia attenuation of metastatic pancreatic cancer.

MEDI 60

SN38-prodrug and nanoparticle-generated hyperthermia show antagonistic effects when co-delivered to a murine model of pancreatic cancer

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Several chemotherapeutic drugs have shown synergistic effects with hyperthermia in treating various cancers. Irinotecan has been shown to be one of these thermochemotherapeutic prodrugs. Carboxylesterase cleaves irinotecan to SN38, which is the active metabolite of irinotecan. Previously we have demonstrated a cell-delivered-nanoparticle-generated (CDNG) hyperthermia system that substantially increases

survival in a murine metastatic pancreatic cancer model that uses tumor homing monocyte/macrophage-like cells (Mo/Ma) to deliver magnetic nanoparticles directly and specifically to tumor sites for alternating magnetic field induced hyperthermia. We have also previously demonstrated a self-contained enzyme/prodrug therapy that uses the same tumor homing monocyte/macrophage-like cells to deliver an SN38-Dextran prodrug and an inducible carboxylesterase gene that also increases survival in the same model. Therefore, both systems were combined and co-loaded into Mo/Ma and co-delivered to a murine metastatic cancer model. Surprisingly, the SN38 treatment and the nanoparticle treatment showed strong antagonism with nearly complete suppression of treatment effect.

MEDI 61

Design and synthesis of chromones as novel antimelanoma agents

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Late-stage malignant melanoma is difficult to treat by present chemotherapies; therefore, there is a dire need to find new chemotherapies for melanoma. Our laboratory is focused on the discovery of novel anticancer agents for melanoma (Li et al 2007, Chen et al 2008, Lu et al 2008, and Zhao et al 2009). In an effort to find out new small molecules as anti-melanoma agents, we screened a library of compounds from the University of Cincinnati and identified two compounds, 7-(4-Bromocarbonyl-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,2,3,4-tetrahydro-quinoline-3-carboxylic acid and 2-Amino-4-(5-bromo-2-methoxy-phenyl)-7-hydroxy-4H-chromene-3-carbonitrile as initial hits. 7-(4-Bromocarbonyl-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,2,3,4-tetrahydro-quinoline-3-carboxylic acid being an alkylating agent, we are highly interested in the chromenes and the chromene scaffold have been well represented within potent anti-cancer agents (Kemnitzer et al 2008, 2004). This synthetically feasible scaffold will serve as a starting point in our program to find highly potent new anti-melanoma agents by synthesizing a new library of chromenes and evaluating them for activity against melanoma.

MEDI 62

Novel inhibitors of Mer kinase as potential anticancer agents in the treatment of acute lymphoblastic leukemia (ALL)

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Acute lymphoblastic leukemia (ALL) is the most common cancer in children, representing 23 percent of cancer diagnoses among children younger than 15 years of age. Ectopic Mer expression in T-cell ALL is suspected to be responsible for drug resistance in children and Mer kinase inhibitors may act as chemosensitizers to increase efficacy and reduce toxicities of current regimens in this disease. We took the advantage of known X-ray crystal structure of Mer by using structure based design built our compound library. The small compounds with a pyrazolopyrimidine core structure from this library exhibited selective inhibitory activity on Mer among the Tyro3/Axl/Mer (TAM) family of receptor tyrosine kinases. Sub-nanomolar specific Mer inhibitors have been discovered through the Hit-to-Lead modification process. Optimization of the physical properties towards clinical candidates is under investigation.

MEDI 63

Bioluminescent blue light for photodynamic therapy for different types of cancer

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The biggest obstacle for photodynamic therapy for deeply-seated tumors is poor light penetration through the human body. *In situ* generation of blue light by employing tumor-homing stem cells may be able to overcome this obstacle. 5-Aminolevulinic acid is used by cells for the biosynthesis of protoporphyrin IX, which can be effectively used as photosensitizer. We have demonstrated that neural stem cells (NSC) and rat umbilical cord matrix-derived stem cells (RUCMSC) home to B16F10 and 4T1 tumors. We have transiently transfected tumor-homing mouse NSC and RUCMSC with *Gaussia* luciferase (gluc), and injected these cells intravenously into C57BL/6 mice bearing B16F10 tumors. These stem cells have accumulated in the tumor tissue and expressed gluc *in vivo*. Upon intravenously administering coelenterazine, the gluc's substrate, intense bioluminescence ($\lambda_{\max}=480\text{nm}$) occurs which is absorbed by protoporphyrin IX. Both *in vitro* and *in vivo* data show that this novel approach for photodynamic therapy can be applied for the treatment of deep-seated tumors.

MEDI 64

Fragment based approach to targeting the Rad51:BRCA2 protein-protein interaction

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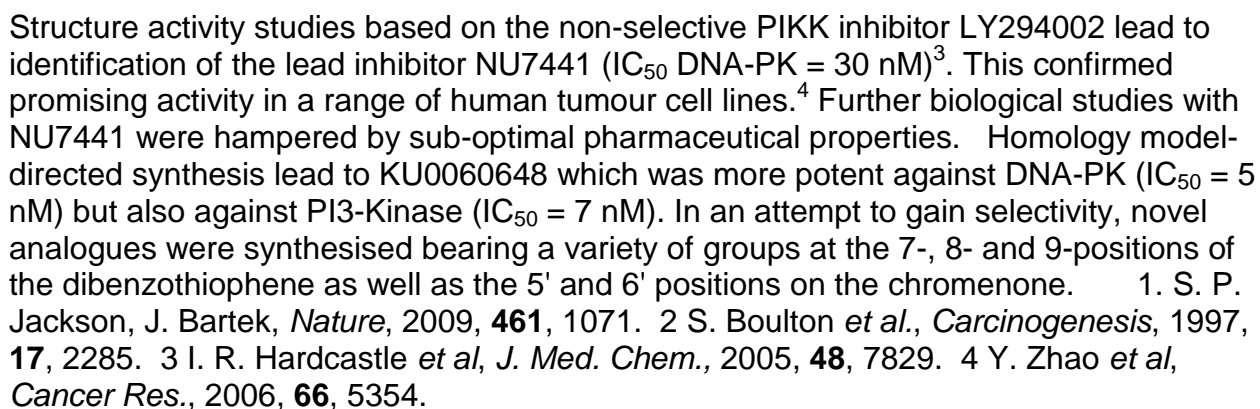
Anthony G. Coyne, *agc40@cam.ac.uk*, Department of Chemistry, University of Cambridge, CB2 1EW, United Kingdom; Duncan E. Scott,⁽¹⁾ Chris Abell,⁽¹⁾ May Marsh,⁽²⁾ Marko Hyvonen,⁽²⁾ Tom L. Blundell,⁽²⁾ Ashok Venkitaraman.⁽³⁾ (1) Department of Chemistry, University of Cambridge, CB2 1EW, UK. (2) Department of Biochemistry, University of Cambridge, Tennis Court Road, Cambridge, UK CB2 1GA, United Kingdom. (3) Cambridge Molecular Therapeutics Programme, Hutchison/MRC Research Centre, University of Cambridge, Hills Road, Cambridge, CB2 0XZ, United Kingdom The druggability of protein-protein interaction sites has been of enormous interest to medicinal chemists in recent years. However there has been only moderate success in discovering small molecules that can disrupt such interactions. One of the approaches that has proven successful is using fragment based drug discovery. We are interested in targeting the Rad51:BRCA2 protein-protein interaction using fragment based approaches. The Rad51:BRCA2 interaction is clinically important as it is essential for DNA repair by homologous recombination which is a key cellular pathway involved in the resistance of cancer cells to ionizing radiation. Inhibition of this interaction will render cells unable to repair DNA damage and in conjunction with other drugs enable a method to target cancer cells. We will report the results of our fragment screening work against this protein-protein interaction and our attempts to develop small molecules to target this interaction. We will show that a combination of synthetic chemistry, structural biology and biophysical techniques, as part of the fragment based approach, can be used to disrupt these challenging targets.

MEDI 65

Development of potent inhibitors of DNA-dependent protein kinase (DNA-PK)

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The serine/threonine kinase DNA-dependent protein kinase (DNA-PK) is a member of the phosphatidylinositol 3-kinase related kinase (PIKK) family of enzymes, and plays an important role in DNA double-strand break (DSB) repair.¹ ATP-competitive DNA-PK inhibitors may, therefore, be useful as agents to improve the activity of radio- and chemo-therapy by preventing the repair of DNA damage in cancer cells.²



Novel hydroxyethyl-, and methylpyrazoline derivatives of acetyl-combretastatin

A4: Synthesis, structural analysis, and biological evaluation

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Combretastatin A4 (CA-4) is a stilbene naturally occurring anticancer product isolated from *Combretum caffrum*. It exhibits a wide range of biological functions including the inhibition of tubulin polymerization. CA-4 is, however, impaired by its poor solubility in water and cell culture media. As a result, there is an intense effort underway in the design, synthesis, and testing of novel CA-4 analogs that exhibit comparable activity to CA-4 itself but exhibit enhanced water solubility. Efforts in our laboratory are focused on developing a novel class of CA-4 analogs with enhanced water solubility. The target compounds in this study contain a polar group, such as hydroxyethyl or methylpyrazoline, and are derived from a previously unknown acetyl-CA-4. The rationale, synthesis, structural analysis, and the ability of the target compounds to inhibit the growth of murine lymphoma (L1210), melanoma (B16), and human melanoma

MDA-MB-435 cells will be described, along with their ability to cause microtubule depolymerization in cells.

MEDI 67

Non-ATP competitive CDK2 cyclin groove inhibitors through REPLACE mediated fragment assembly

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A strategy for fragment based design of protein-protein interaction inhibitors which provides advantages over conventional methods was recently proposed and validated. REPLACE (Replacement with Partial Ligand Alternatives through Computational Enrichment) is an iterative approach for generating fragment alternatives to known peptide determinants. We further exemplify this approach through the optimization of individual partial ligand alternatives and generate more pharmaceutically relevant and non-ATP competitive inhibitors of the CDK2/cyclin A substrate recruitment binding site by combining these fragments. A diverse set of substituted aryl heterocycles replacing a critical charge-charge interaction were synthesized and provided insights into the H-bonding requirements of the cyclin groove. In addition the structure-activity relationship of a bisarylether system replacing a phenylalanine determinant has been developed while allowing increased complementarity with the hydrophobic pocket. This work further validates REPLACE as an effective strategy for converting peptidic compounds to more drug-like and non peptide compounds for inhibition of protein-protein interactions.

MEDI 68

Investigations of various heterocycles to improve metabolic stability within a series of PI3K/mTOR dual inhibitors

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Many human cancers have activated phosphoinositide 3-kinase (PI3K) signaling, often as a result of gain-of-function mutations in PI3Ka or loss-of-function mutations in PTEN (a phosphatase that performs the reverse phosphorylation event performed by Class I PI3Ks). These genetic alterations strongly link constitutive PI3K signaling to

tumorigenesis and have stimulated an interest in targeting PI3Ka, and other kinases in the PI3K/Akt pathway, for the treatment of cancer. We have recently reported on *N*-(6-(6-chloro-5-(4-fluorophenylsulfonamido)pyridin-3-yl)benzo[d]thiazol-2-yl)acetamide which is a potent and efficacious inhibitor of PI3Ka and mTOR in vitro and in vivo. However, in hepatocyte and in vivo metabolism studies, this compound was found to undergo deacetylation on the 2-amino substituent of the benzothiazole core. As an approach to reduce or eliminate this metabolic deacetylation, a variety of analogs were examined as an alternative to the benzothiazole ring. In vitro studies of these analogs will be presented as well as in vivo data on advanced compounds. **Keywords:** Phosphoinositide 3-kinase, PI3K, mTOR, Akt, hepatocyte

MEDI 69

Identification of non-amidine inhibitors of acid-sensing ion channel-3 (ASIC3)

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The search for novel treatments for chronic pain and inflammation continues to be an area of medical need. Under conditions of acidosis, tissue damage often results leading to acute or chronic pain. Numerous receptors and ion channels expressed in neurons have been shown to be modulated by protons. Among them, the acid-sensing ion channel-3 (ASIC3) is representative of a proton-gated subgroup of degenerin/epithelial Na⁺ cation channel family. There is substantial evidence that ASIC3 serves as a pH sensor playing an important role in conveying the pain sensation resulting from tissue acidosis. Accordingly, small molecule inhibitors of the ASIC3 channels are of considerable interest to study the physiological role of ASIC3. This paper describes efforts to identify non-amidine chemotypes from existing leads in an effort to identify potent blockers to advance the therapeutic evaluation of ASIC3 inhibition.

MEDI 70

Structural modification of neuroprotective small molecules for target identification studies: Toward possible amyotrophic lateral sclerosis therapeutics

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Amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease is a neurodegenerative disorder affecting an estimated 87,000 people worldwide. ALS is characterized by rapid and progressive loss of motor function, leading to paralysis and resulting in death, on average within 3-5 years. Riluzole is currently the only approved treatment for ALS and extends survival, on average by only 2-3 months. The need for the development of further therapeutic options for this disease is apparent. Our laboratories have developed lead compounds with demonstrable activity in G93A-SOD1 mice models of ALS. We present herein, ongoing efforts to both investigate further the pharmacophore with structure activity relationship studies and the modification of these leads to be amenable to target identification studies by a range of chemical and molecular biological techniques.

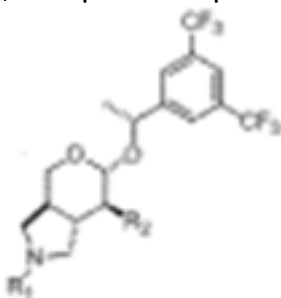
MEDI 71

Octahydropyrano[3, 4-c]pyrrole NK1 receptor antagonists

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The substance-P-preferring neurokinin receptor (NK1) is present in high concentration in areas of the brain that mediate many important biological functions. In an efforts to discover highly potent and selective NK1 antagonists for chemotherapy-induced nausea and vomiting (CINV), we had identified a new class of NK₁ receptor antagonists with an octahydropyrano[3, 4-c]pyrrole core. This series of NK1 antagonists, for which SAR around R1 and R2 will be presented, had many attractive properties including potent NK1 inhibition in the presence of human serum, excellent functional activity, and good pharmacokinetic properties. In addition, many compounds in this series displayed high

NK₁ receptor occupancy for 24 hours as assessed by the gerbil foot tapping model.



MEDI 72

WY-50295: Improved synthesis of a starting point for Alzheimer's disease drug discovery

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Recent data show that genetic or pharmacological inhibition of the enzyme 5-lipoxygenase (5-LO) reduces levels of neurotoxic beta-amyloid peptides and plaque deposition in Tg2576 mice, a transgenic model of Alzheimer's-like amyloidosis. This occurs through a novel mechanism that involves decreased expression of gamma secretase, one of the enzymes responsible for the improper metabolism of amyloid precursor protein thought to underlie Alzheimer's pathology. This reduction in gamma secretase is not accompanied by a reduction in Notch-1 processing, a liability seen with known gamma secretase inhibitors. An alternate route to achieve this result that has not been explored is to inhibit 5-lipoxygenase activating protein (FLAP), a cofactor required for 5-LO activity. FLAP inhibitors are known but do not penetrate the CNS because of their high molecular weight and high polar surface area. We recently developed an improved synthesis of WY-50295, a suspected FLAP inhibitor. Here we present that improved synthesis as well as our plans to enhance the CNS penetration of WY-50295 through a prodrug approach in order to develop tool molecules that can be used to assess the potential CNS therapeutic utility of FLAP inhibitors.

MEDI 73

Small molecule discovery: Phenylalkylamine-benzenesulfonamides as 5-HT₆ receptor ligands

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To investigate the binding conformation of phenylalkylamine-benzenesulfonamides relative to ergolines. The hypothesis tested was that: *since sulfonamide-arylalkylamines bind to 5-HT₆ in an extended ergoline type of conformation, phenylethylamines, phenylpiperazines and pyrroloethylamines bearing the appropriate substituents should also bind.* **Rationale:** 5-HT₆ is a GPCR (g-protein coupled receptor) found almost exclusively in the brain, whose biological role is still unclear. In order to probe this receptor's role in CNS disorders (Alzheimer's, schizophrenia, anxiety, convulsive, satiety, etc.) small molecules with selective activity (agonist or antagonist) at this receptor are desired. Because of the privileged location of 5-HT₆, drugs targeting this receptor would lack peripheral side effects. **Methodology:** Several compounds were rationally designed using structural information from reported ligands (Ro 04-6790, SB-271046, and MS-245), synthesized, characterized elementally and by NMR studies, and evaluated for activity at 5-HT₆ using in vitro binding affinity assays.

Findings/conclusions: 1) We identified phenylethylamines, phenylpiperazines and pyrroloethylamines as novel 5-HT₆ ligands. These simpler structures can serve as templates for generating even more ligands for this receptor. 2) These novel structures bind to 5-HT₆ receptors with reasonably high affinities. 3) Since arylethylamines bind in the ergoline extended conformation, these compounds also bind with the same conformation.

MEDI 74

Discovery of imidazoles as potent calcitonin gene-related peptide (CGRP) antagonists

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Calcitonin gene-related peptide (CGRP), a 37-amino acid peptide belonging to a family of structurally-related peptides which includes adrenomedullin and amylin, has been implicated in the pathogenesis of migraine. In an earlier paper, we disclosed our intranasal (IN) development candidate BMS-694153. Although potent, compounds from this series lacked the bilayer permeability required to support oral dosing. In an effort to decrease solvation by water, a core amide was replaced with a number of novel heterocyclic replacements. A promising imidazole-containing series was identified. Several analogues were identified which maintained excellent potency and improved cell permeability.

MEDI 75

Glutamate isosteres showing selectivity toward the vesicular glutamate transporter vs. the obligate exchange transporter, system x_c⁻

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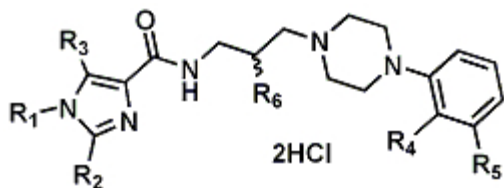
The vesicular glutamate transporter (VGLUT) regulates uptake of glutamate (*L*-Glu) between cytosolic and luminal compartments. System x_c^- (Sx_c^-), a chloride-dependent, sodium-independent obligate exchanger, couples the export of intracellular *L*-Glu with the import of extracellular *L*-cystine. We previously acquired evidence that VGLUT but not other glutamate transporters (e.g., EAATs) were inhibited by structures containing a weakly basic α -amino group. To test this hypothesis, we prepared a series of glutamate analogs in which weak amide and amide-containing isosteres were used in place of the α -amino acid group and analyzed as inhibitors of VGLUT and system x_c^- . Of numerous analogs prepared, two were found to be relatively strong inhibitors of VGLUT reducing uptake to less than 6% of control at 5 mM but few analogs inhibited system x_c^- greater than 50% of control. In sum, amide-containing isosteres of glutamate adds the requisite chemical properties needed to produce selective inhibitors of VGLUT.

MEDI 76

Synthesis and biological evaluation of novel arylpiperazine-containing imidazole 4-carboxamide derivatives: Targeting serotonin 5-HT_{2A/2C} and the serotonin transporter as a potential antidepressant

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Serotonin antagonist / reuptake inhibitor (SARI) drugs that block both the serotonin 5-HT₂ receptors and the serotonin transporters have been developed. The human 5-HT_{2A} or 5-HT_{2C} receptor has been implicated in several neurological conditions, and potent and selective 5-HT_{2A/2C} ligands may have therapeutic potential for treatment of CNS diseases, such as depression. Therefore, the 5-HT_{2A/2C} receptors have been considered as reasonable targets for the improved treatment of depression. On the other hand, an imidazole moiety usually provides good pharmacokinetic properties as a drug substance. And the most frequently studied of arylpiperazine analogues have been found as serotonin receptor ligands, especially 5-HT_{1A} and 5-HT_{2A} ones. Accordingly, we synthesized and evaluated arylpiperazine-containing imidazole 4-carboxamide derivatives against serotonin receptor (5-HT_{2A/2C}) antagonists and serotonin reuptake inhibition. Some of the compounds show excellent IC₅₀ values and antidepressant-like effect in *in vivo* forced swimming test (FST). Based on these results, further lead optimization studies resulted in identifying promising compounds for potentially therapeutic use.



MEDI 77

Discovery of pyrrolo[2,3-*d*]pyrimidin-4-ones as corticotropin-releasing factor 1 receptor antagonists with a carbonyl-based hydrogen bonding acceptor

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A new class of pyrrolo[2,3-*d*]pyrimidin-4-one corticotrophin-releasing factor 1 (CRF₁) receptor antagonists has been designed and synthesized. In general, reported CRF₁ receptor antagonists possess a sp²-nitrogen atom as hydrogen bonding acceptor (HBA) on their core scaffolds. We proposed to use a carbonyl group of pyrrolo[2,3-*d*]pyrimidin-4-one derivatives as a replacement for the sp²-nitrogen atom as HBA in classical CRF₁ receptor antagonists. As a result, several pyrrolo[2,3-*d*]pyrimidin-4-one derivatives showed CRF₁ receptor binding affinity with IC₅₀ values in the submicromolar range. *Ex vivo* ¹²⁵I-sauvagine binding studies showed that 2-(dipropylamino)-3,7-dimethyl-5-(2,4,6-trimethylphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (30 mg/kg, po) was able to penetrate into the brain and inhibit radioligand binding to CRF₁ receptors (frontal cortex, olfactory bulb, and pituitary) in mice. We identified pyrrolo[2,3-*d*]pyrimidin-4-one derivatives as the first CRF₁ antagonists with a carbonyl-based HBA.

MEDI 78

Discovery of XEN907, a spirooxindole blocker of Na_v1.7 for the treatment of pain

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Starting from the oxindole **2a** identified through a high-throughput screening campaign, a series of Na_v1.7 blockers were developed. Following the elimination of undesirable structural features, preliminary optimization of the oxindole C-3 and N-1 substituents afforded the simplified analogue **9b**, which demonstrated a 10-fold increase in target potency vs. the original HTS hit. A scaffold rigidification strategy then led to the discovery of XEN907, a novel spirooxindole Na_v1.7 blocker. This lead compound, which in turn showed a further 10-fold increase in potency, represents a promising structure for further optimization efforts.

MEDI 79

Novel amides as potent and selective histamine H₃ receptor antagonists

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H₃ receptors are widely expressed in the mammalian brain, particularly in areas involved in cognitive processes and arousal. They regulate histamine in the brain and also affect the release of other neurotransmitters including dopamine, nor-adrenaline, serotonin and acetylcholine, suggesting their potential utility for the treatment of a variety of cognitive and sleep disorders. Most of the earlier reported dibasic compounds suffer from sub-optimal pharmacokinetic properties like exceptionally long half-life in both rat and dog. We report our initial findings towards identification of novel aryl/heteroaryl amide compounds as potent and selective H₃ receptor antagonists. The series has favorable pharmacokinetic properties (half life ~ 1 hr with adequate oral exposure), no CYP liability and excellent brain penetration. The lead compound showed dose dependent receptor occupancy and elevate monoamines in microdialysis assay and is active in preclinical rodent models of cognition. It also blocks R- α -methyl histamine induced water intake. The design, synthesis, SAR and pharmacological profile of these new analogs as potential treatments for cognitive dysfunction will be presented.

MEDI 80

Novel Trolox-C-terminal motifs of A β 42 as neuroprotective agents for the treatment of Alzheimer's diseases

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The aggregation pathway of β -amyloid (A β) is a key target to prevent or delay the onset of Alzheimer's diseases. Because the aggregation of the 40-mer and 42-mer peptides (A β 40, A β 42) has been suggested to contribute to oxidative stress that is responsible for neurotoxicity. Interestingly, the aggregative ability and neurotoxicity of A β 42 are considerably greater than those of A β 40, probably due to its high lipophilic C-terminal domain. In this work, novel multifunctional antioxidants were designed by combining Trolox, the aromatic portion of vitamin E responsible for radical capture, and the C-terminal motifs that would be expected for high affinity to A β 42. They effectively protected SH-SY5Y neuroblastoma cells against A β 42-induced damage. They also showed antioxidative properties as well as vitamin E, and surprisingly strong inhibitory

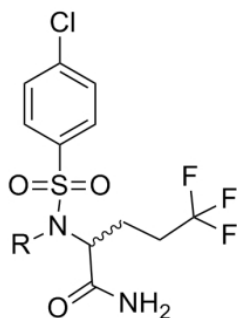
activities on A β 42 aggregation, emerging as promising molecules for neuroprotection by suppressing the mechanism of free radical generation via aggregation of A β .

MEDI 81

Substituted cyclic ether arylsulfonamides as potent inhibitors of γ -secretase

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Alzheimer's Disease (AD) is the most common form of senile dementia affecting 24 million people worldwide. It is hypothesized that the A β peptide is the primary factor causing AD. This peptide is formed through the proteolytic cleavage of the amyloid- β -precursor protein (APP) by β -secretase (BACE1) and γ -secretase. Reduction of A β production through the substitution of γ -secretase is therefore one strategy explored since the mid 90s to slow progression of Alzheimer's disease. We herein disclose our SAR studies into a novel series of sulfonamide containing γ -secretase inhibitors. This series of compounds contains range of substituted cyclic ethers in the left hand portion of the molecule.



R = various substituted cyclic ethers

MEDI 82

γ -Secretase modulators: Alternatives for the imidazole moiety

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Gamma-secretase modulation has been proposed as a potential disease modifying anti-Alzheimer's approach. In contrast to γ -secretase inhibitors, modulators cause a product shift from the longer amyloid isoforms to shorter, more soluble and less amyloidogenic isoforms, without inhibiting NOTCH proteolytic processing. Two main classes of γ -secretase modulators (GSM) have been described: NSAID derived carboxylic acids and non-carboxylic acid compounds.¹ Most compounds from the latter class have an N-(hetero)aryl-imidazole moiety in common, which seems to be crucial for optimal potency. Since many of these compounds display undesired properties, such as CYP450 and hERG channel inhibition, replacement of the imidazole ring with other heterocycles was investigated. The SAR which has emerged from this research will be presented. This has resulted into non-imidazole, non-carboxylic acid containing GSM compounds with high in vitro and in vivo potency. 1) Oehlrich, D.; Berthelot, D. J.-C. Gijzen, H.J.M. *J. Med. Chem.* **2011**, 54, 669-698

MEDI 83

Synthesis and preliminary evaluation of substituted N-aryl-piperazine based compounds as muscarinic ligands

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The various subtypes of muscarinic receptors (M_1 - M_5) have a wide range of physiological effects that includes controlling smooth muscle tone to neurotransmitter release in the CNS. Hence these receptor subtypes have been investigated as potential therapeutic targets for agents capable of treating Alzheimer's Disease, Parkinson's Disease, peptic ulcer disease, COPD, urinary incontinence, and muscle spasms. Molecular modification of lead 5-substituted 4,5-dihydro-3,3-diethyl-2(3H)-furanones has been undertaken providing a series of lactone-based muscarinic ligands which feature N-aryl piperazines as key fragments. Microwave-assisted synthesis of various sterically hindered N-aryl piperazines has been developed allowing quick access to structurally diverse muscarinic ligands. The novel synthetic methods to the target ligands, the results of preliminary binding studies, and the structure activity relationship for the series are discussed.

MEDI 84

Synthesis of carbon-11-labeled arylpiperazinylalkylthiobenzoxazole derivatives as new potent and selective 5-HT_{1A} serotonin receptor PET radioligands

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Serotonin (5-HT) is an important neurotransmitter. 5-HT family contains 14 serotonin receptor (5-HTR) subtypes. Among 5-HTRs, 5-HT_{1A} is one of the most studied subtypes

and is involved in anxiety and depression. Recent reports indicate that 5-HT_{1A}R agonists have neuroprotective properties, and 5-HT_{1A}R antagonists could be useful in the treatment of Alzheimer's disease. A new series of arylpiperazinylalkylthiobenzoxazole derivatives has been recently developed by Siracusa et al. as potent and selective 5-HT_{1A} serotonin receptor ligands, these compounds showed excellent binding affinity with nanomolar *K_i* values and selectivity for 5-HT_{1A}R over both α_1 and D₂ receptors. New carbon-11-labeled arylpiperazinylalkylthiobenzoxazole derivatives were first designed and synthesized as radioligands for biomedical imaging technique positron emission tomography (PET) to image 5-HT_{1A}R. Unlabeled arylpiperazinylalkylthiobenzoxazole derivatives (precursors and standards) were synthesized from benzo[d]oxazole-2-thiol, 5,7-dimethyl benzo[d]oxazole-2-thiol; 1-bromo-4-chlorobutane, 1-bromo-6-chlorohexane; and 1-(2-methoxyphenyl)piperazine, 2-(piperazin-1-yl)phenol in 2 steps with moderate yields. The target tracers, 2-((4-(4-(2-[¹¹C]methoxyphenyl)piperazin-1-yl)butyl)thio)benzo[d]oxazole, 2-((4-(4-(2-[¹¹C]methoxyphenyl)piperazin-1-yl)butyl)thio)-5,7-dimethylbenzo[d]oxazole, 2-((6-(4-(2-[¹¹C]methoxyphenyl)piperazin-1-yl)hexyl)thio)benzo[d]oxazole, and 2-((6-(4-(2-[¹¹C]methoxyphenyl)piperazin-1-yl)hexyl)thio)-5,7-dimethylbenzo[d]oxazole, were prepared from their corresponding precursors, 2-(4-(4-(benzo[d]oxazol-2-ylthio)butyl)piperazin-1-yl)phenol, 2-(4-(4-((5,7-dimethylbenzo[d]oxazol-2-ylthio)butyl)piperazin-1-yl)phenol, 2-(4-(6-(benzo[d]oxazol-2-ylthio)hexyl)piperazin-1-yl)phenol, and 2-(4-(6-((5,7-dimethylbenzo[d]oxazol-2-ylthio)hexyl)piperazin-1-yl)phenol, with [¹¹C]CH₃OTf through O-[¹¹C]methylation and isolated by a simplified solid-phase extraction (SPE) method using a Sep-Pak® Plus C18 cartridge in 50-60% radiochemical yields decay corrected to end of bombardment (EOB) based on [¹¹C]CO₂, with 185-370 GBq/μmol specific activity at end of synthesis (EOS).

MEDI 85

Synthesis of novel benzothiophene selective estrogen receptor modulators (BT-SERMs) that provide neuroprotection by a novel GPR30-dependent mechanism

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A family of novel benzothiophene selective estrogen receptor modulators (BT-SERMs) was synthesized. Their structure-activity relationships for neuroprotection displayed a spectrum of ER α and ER β binding affinity and agonist/antagonist activity, thus leading to discovery of a neuroprotective pharmacophore that is present in the clinically relevant SERMs, raloxifene, and desmethylarxoxifene (DMA). The 2-(4'-hydroxyphenyl)-benzo[b]thiophen-6-ol core (BTC) is readily oxidized to a diquinone methide that acts as a Michael acceptor toward cysteine, while the derivatives lacking 4'-hydroxyl group in the 2-phenyl substituent cannot undergo bioactivation to diquinone methides, which

indicates that the receptor mediating neuroprotective activity of BT-SERMs could potentially be activated by Michael addition or, alternatively, by simple noncovalent binding. Collective evidence suggests that the activity of neuroprotective BT-SERMs is GPR30-dependent and ER-independent, and not mediated by antioxidant effects. Comparison of novel BT-SERM derivatives and analogues identified a neuroprotective pharmacophore applicable for design of novel neuroprotective agents with a spectrum of ER activity.

MEDI 86

Synthesis and biological evaluation of selective Tau binders as PET imaging agents for the detection of Alzheimer disease

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Alzheimer's disease (AD) is the leading cause of dementia and the sixth leading cause of death in the US. Postmortem examinations of dementia patient's brains confirm the presence of AD through the detection of extracellular β -amyloid deposits and intracellular neurofibrillary tangles (NFT) that are derived from filaments of abnormal hyperphosphorylated microtubule associated Tau proteins. The presence and severity of NFTs appear to correlate with the severity of dementia and cognitive impairment. In order to develop a non-invasive positron emission tomography (PET) molecular imaging agent that can identify NFT's associated with AD, we have synthesized a series of compounds that bind to Tau but not to β -amyloid. Selected candidates were labeled with [F18] and tested on human AD brain sections. Discussion of SAR, in vitro biological data and in vivo PET imaging results will be presented.

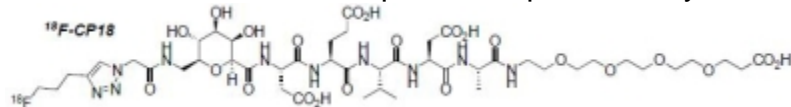
MEDI 87

Discovery of a substrate-based ^{18}F -labeled apoptosis biomarker for PET imaging

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Apoptosis or programmed cell death plays a crucial role in many diseases and their treatments. It is mediated and regulated by a complex signaling cascade involving a number of proteases, most importantly members of the caspase family. An ^{18}F -labeled biomarker (^{18}F -CP18) for *in vivo* positron emission tomography (PET) imaging of apoptosis was designed based on the natural substrate (DEVD) of caspase-3, an

enzyme that plays a key role in the apoptotic process. Additional changes to the substrate were made to improve cell permeability, biodistribution, and clearance.



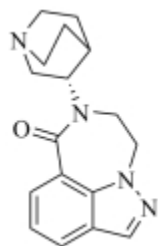
The comparison between PET imaging of various xenograft tumors in mice with immuno staining showed a good correlation ($R^2=0.82$) of ^{18}F -CP18 uptake in apoptotic areas. Further evaluation of this tracer indicates good *in vivo* stability, distribution, and clearance, which makes CP18 a favorable candidate for *in vivo* apoptosis imaging.

MEDI 88

Discovery of diazepinone-based 5-HT₃ receptor partial agonists for the potential treatment of irritable bowel syndrome

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Based on the principle that a weak partial agonist can attenuate the action of endogenous agonist without fully blocking receptor function, we have discovered novel 5-HT₃ receptor partial agonists bearing diazepinone cores that are predicted to show improved therapeutic benefit in the treatment of irritable bowel syndrome over the established 5-HT₃ receptor antagonists. Examples within this chemical series exhibit nanomolar binding affinity for the *h*5-HT_{3A} receptor and a range of agonist responses in HEK293 cells expressing the *h*5-HT_{3A} receptor.



- Binding: *h*5-HT_{3A} K_i = 8 nM
- Partial Agonist Response (relative to 3 μM 5-HT) = 19%

MEDI 89

Development of inhalable antibiotics for the treatment of TB

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The goal of this project is the development of unit-dose, inhalable, antibiotic microparticles and nanoparticles for use in primary and combined therapy approaches to treating tuberculosis (TB) and highly drug-resistant strains of *Mycobacterium tuberculosis* (Mtb) that result in multi drug-resistant (MDR-TB) and extensively drug-resistant TB. Targeted to the alveolar space by merit of high fine particle fractions (FPF) in the $<3.3\ \mu\text{m}$ range, these antibiotic microparticles and nanoparticles utilize the same inhalation pathway as Mtb, to deliver antibiotic to protected TB lesions. This study explores strategies of combining microparticles and nanoparticles with polymer and excipients to improve the fine particle fraction and deliver a larger fraction of antibiotic to the deep lung. Using inhalable antibiotics in combination with more traditional treatment may also provide a strategy for reducing treatment times by potentially increasing the targeted dose to mucosal surfaces and tissue of the airways while reducing systemic side effects.

MEDI 90

Molecules containing reactive peroxide or nitric oxide species for the treatment of malaria

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Malaria continues to be an epidemic in developing countries, and parasite resistance to existing treatments remains a constant threat. It is therefore imperative that new treatments are continually sought, ideally those that can target a number of different pathways exclusive to the parasite. Proliferation of malaria parasites is known to involve several redox pathways, affording the opportunity for redox-active molecules to interfere with such proliferation. To that end, molecules based on the natural product artemisinin (**1**, Figure 1), which contains a reactive peroxide linkage, have been developed that enhance the innate activity of the structure as demonstrated by improved (over existing dosing regimens) curative results in mice. More recently, molecules that generate nitric oxide have shown activity against a variety of parasitic diseases, including malaria. A nitric oxide-generating furoxan ring (**2**, Figure 1) has been hybridized with known antimalarial compounds such as chloroquine and amodiaquine in an attempt to target multiple redox pathways while also blocking resistance against similar quinoline-like molecules. Several mechanisms of action for both artemisinin and nitric oxide have been proposed, though each is thought to target separate pathways. The biological results show that artemisinin continues to be an important chemotype from which new antimalarials should be developed, and that nitric oxide donor hybrids represent a potential new class of drugs.

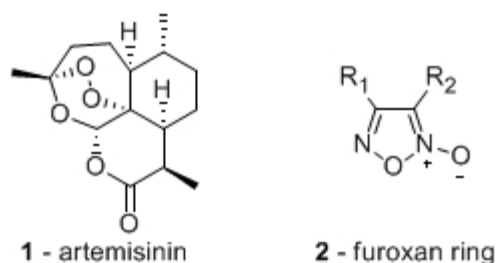


Figure 1 - Structures of molecules containing reactive species

MEDI 91

Virulence-attenuating inhibitors of streptokinase (SK) expression in Group A streptococcus (GAS): Activity optimization and target identification

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Traditional antibiotics rely on killing bacteria or interrupting bacterial reproduction, thereby inducing a direct selective pressure for the evolution of antibiotic resistance. If bacterial mechanisms of virulence are inhibited instead, the host could in principle be protected long enough for clearance by the immune system, eliminating the selective pressure for resistance. SK has been identified as a critical virulence factor in GAS; it allows the bacteria to activate human plasmin and dissolve fibrin-rich clots the host creates around sites of invasion. High-throughput screening (HTS) identified a compound able to interfere with the transcription of the SK gene by GAS. Our group has undertaken an effort to optimize the activity and pharmacokinetic competence of this lead, as well as the synthesis of a variety of affinity probes probes designed to identify the macromolecular target of this scaffold.

MEDI 92

Synthesis of analogs with phenanthroline functionality targeting biosynthesis of lipid A in various gram-negative bacteria

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Pseudomonas aeruginosa (*P. aeruginosa*) and many other Gram-negative opportunistic pathogens continue to plague hospitals causing nosocomial infections. Due to the continual resistance towards commercially available antibiotics, there is a great need for a new generation of antibiotics. One promising target is the zinc-dependent metalloamidase, UDP-3-O-(*R*-3-hydroxymyristoyl)-*N*-acetylglucosamine deacetylase

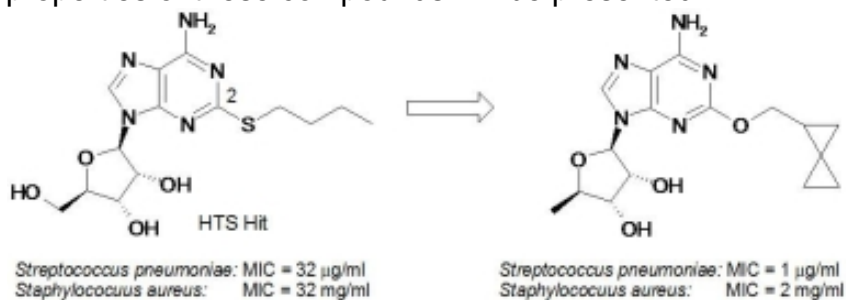
(LpxC), which is the first committed step of Lipid A biosynthesis in Gram-negative bacteria. LpxC is an essential enzyme that is coded by a single copy gene that is conserved in almost all Gram-negative bacteria. We here report the synthesis of small molecules including 3-(1H-imidazo[4,5-f][1,10]phenanthroline-2-yl)phenol (HIPP), 2-(4-(hexyloxy)phenyl)-1H-imidazo[4,5-f][1,10]phenanthroline (HPHIP), and 2-(3-(heptyloxy)phenyl)-1H-imidazo[4,5-f][1,10]phenanthroline (HPIP) which easily coordinate with metals including zinc. In addition, we report our modeling experiments have shown an enhanced binding affinity of these compounds with the active site of *P. aeruginosa* LpxC.

MEDI 93

Synthesis, SAR, and optimization of DMPK properties of 2-substituted adenosine derivatives as bacterial NAD⁺-dependent DNA ligase inhibitors

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DNA ligases are essential enzymes for DNA replication, repair and recombination in all organisms. Eubacterial DNA ligase (LigA) requires NAD⁺ for activity, while eukaryotic and most viral DNA ligases require ATP. Because of their essential nature, unique structures and widespread existence, bacterial DNA ligases represent a valuable target for identifying novel and selective antibacterial agents. High throughput screening of the AstraZeneca compound collection identified a class of adenosine analogs as inhibitors of bacterial NAD⁺-dependent DNA ligase. Modifications at the 2-position of the scaffold led to the identification of compounds with low nanomolar enzyme potency and good microbiological activity. The detailed SAR results and our efforts in improving the DMPK properties of these compounds will be presented.



MEDI 94

Evaluation of antimicrobial activity of *Fagara zanthoxyloides* extracts

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The alcohol extracts of the root bark of the plant *Fagara zanthoxyloides* (Lam) were investigated for their antimicrobial activities. *Fagara zanthoxyloides* is part of the Rutaceae family. It is an indigenous plant that is widely used as chewing stick for tooth cleaning in West Africa. This plant has exhibited inhibitory effects on *Plasmodium falciparum*, one of the species that causes malaria. It also has therapeutic effect on sickle cell anemia, and has anticancer abilities. The paper disc diffusion method using Muller-Hinton agar plates has been used to investigate the antimicrobial activities of the root bark extracts. The inhibitory effect of *F. zanthoxyloides* against the bacterial growth of *Escherichia coli*, Methicillin-Susceptible *Staphylococcus aureus*, Methicillin-Resistant *Staphylococcus aureus*, and *Enterococcus faecium* were investigated in this study. These bacteria present a diverse study group which will allow testing the broad range of activity that the extracts from *F. zanthoxyloides* will have.

MEDI 95

Imidazole diamides as inhibitors of bacterial NAD⁺-dependent DNA ligases

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DNA ligases are enzymes that play a critical role in DNA replication, recombination and repair in living organisms. Bacterial DNA ligase (LigA) shares little sequence homology with eukaryotic DNA ligases, therefore it has been evaluated as an antibacterial target. High throughput screening identified imidazole diamides as selective inhibitors of LigA, showing no inhibitory activity toward human DNA ligase. Co-crystal structures confirmed that imidazole diamides bind in the AMP-binding pocket of the LigA adenylation domain. Parallel synthesis was employed to evaluate the series. Structure-activity relationships were developed around both amides. The compounds prepared had IC₅₀ values ranging from 200µM to 0.4µM.

MEDI 96

HIV attachment inhibitors with measurable aqueous solubility, significant bioavailability, and high potency

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The first step in HIV infection is the attachment of the viral envelope gp120 glycoprotein to CD4 on the surface of the human target cell. Inhibitors of this process provide another potential avenue for viral suppression. Early program lead inhibitors were very potent but suffered from poor oral exposure. It was postulated that low aqueous solubility contributed to the observed low bioavailability. One approach explored for increasing the aqueous solubility of this class of inhibitors was to reduce the number of aromatic rings. Toward this objective, a benzamide moiety was replaced with non-aromatic cyclic urea moieties. The targeted aqueous solubility was obtained without sacrificing a significant level of potency. Subsequent pharmacokinetic studies demonstrated improved oral exposure when dosed in rats.

MEDI 97

Design, synthesis and SAR study of bridged tricyclic pyrimidinone as HIV integrase inhibitors

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Raltegravir is an important addition to the clinical armamentarium of anti-retroviral agents, but resistance to this agent is an emerging issue. One of our objectives for a second generation integrase program is to develop a compound that would be efficacious against viruses resistant to this first generation integrase inhibitor. To that end, we investigated a series of bridged tricyclic pyrimidinones as potential HIV-1 integrase inhibitors. After surveying several bridged tricyclic pyrimidinones as inhibitors of viruses with raltegravir resistant genotypes, the [3.2.2] template was selected for further evaluation and optimization. In this presentation, we disclose the synthesis and antiviral activity of a series of bridged [3.2.2] tricyclic pyrimidinones as novel HIV-1 integrase inhibitors that demonstrate potent activity toward viruses resistant to raltegravir.

MEDI 98

Preclinical drug metabolism and pharmacokinetic evaluation of novel HMDCK prodrugs as potent anti-HIV NNRTIs

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The drug metabolism and pharmacokinetic profiles of ester prodrugs (**2-9**) of HMDCK (**1**) were evaluated. HMDCK is a novel anti-HIV NNRTI functioning by inhibiting the production of HIV-1 dsDNA from ssDNA intermediates. However, the insufficient metabolic stability of HMDCK limits its further clinical development. In the present study, the *in vitro* metabolic stability of prodrugs **2-9** were investigated using Sprague-Dawley rat liver microsomes under oxidative conditions. The L-aniline ester prodrug **7** was the best compound, with an apparent *in vitro* $t_{1/2}$ of 86.63 min and intrinsic clearance (CL_{int}) of 0.080 mL/min/mg. The *in vivo* PK evaluation in male SD rats indicated that **7** exhibited a higher oral bioavailability (F: 25.7%), lower systemic clearance (CL: 0.016 L/min/kg), and moderate MRT (1.793 h). Prodrug **7** also had a better water solubility (18 mg/L) than HMDCK (8.4 mg/L). Overall, these preclinical results supported the further development of **7** as a novel NNRTI.

MEDI 99

SAR study of CD4 mimics targeting the HIV entry mechanism and their hybrid molecules with a CXCR4 antagonist

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Small-molecule CD4 mimics were previously reported as a novel class of HIV-1 entry inhibitors that block the gp120-CD4 interaction and induce a conformational change in gp120, exposing its co-receptor-binding site. In this study, the structure-activity relationship (SAR) study of a series of CD4 mimic analogs was conducted to investigate the contribution from the aromatic and piperidine moieties of CD4 mimic to anti-HIV activity, cytotoxicity, and CD4 mimicry effects on conformational changes of gp120. The results indicate that i) a certain size and electron-withdrawing ability of the *para*-position of the aromatic ring are indispensable for potent anti-HIV activity; ii) the presence of piperidine moiety is important for the CD4 mimicry; and iii) N-substituents of the piperidine moiety contribute significantly to anti-HIV activity and cytotoxicity. In addition, several hybrid molecules based on conjugation of a CD4 mimic analog with a selective CXCR4 antagonist were also synthesized and their utility evaluated.

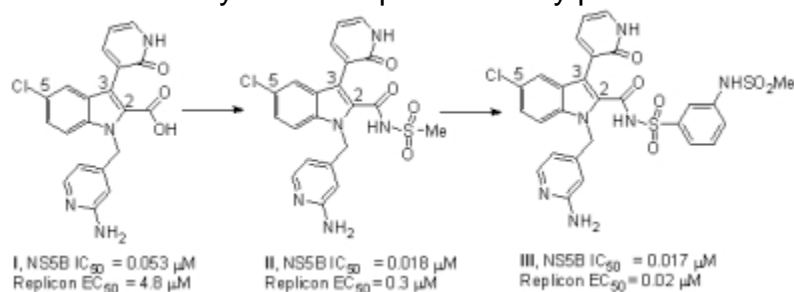
MEDI 100

Novel HCV NS5B polymerase inhibitors: Discovery of indole C2- acyl sulfonamides

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Venkatraman; Bancha Vibulbhan; Charles Lesburg; Jose Duca; Charles McNemar; Sony Agrawal; Eric Ferrari; Chuan-kui Jiang; H.-C. Huang; Neng-Yang Shih; George Njoroge; Joseph A Kozlowski. Merck Research Laboratories, Kenilworth New Jersey 07033, United States

Previous work described a series of novel indole based NS5B palm site polymerase inhibitors exemplified by structure I. Further structure – HCV NS5B binding activity relationship at the indole C2 position revealed a distinct subseries with biosiosteric C2 acyl sulfonamides (II) as replacements of C2 carboxylic acids. The optimization campaign resulted in the discovery of extended C2 acyl sulfonamide derivatives (III) with nanomolar enzyme and replicon activity profile.

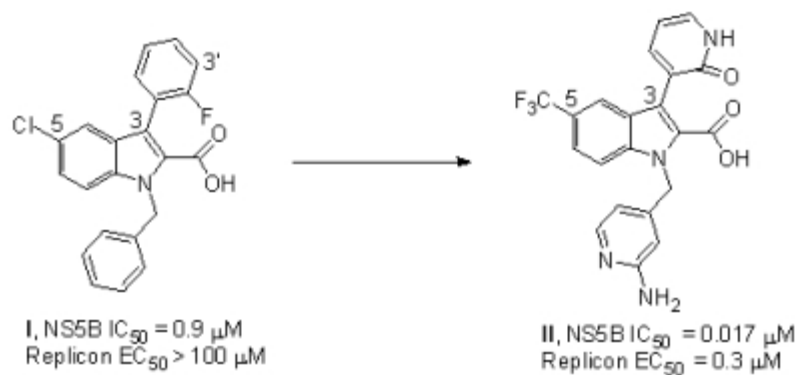


MEDI 101

Novel HCV NS5B polymerase inhibitors: Discovery of indole 2- carboxylic acids with C3-heterocycles

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SAR development of indole-based palm site inhibitors of HCV NS5B polymerase exemplified by initial indole lead I (NS5B IC_{50} = 0.9 mM, replicon EC_{50} >100 mM) is described. Structure-based drug design led to the incorporation of novel heterocyclic moieties at the indole C3-position which formed a bidentate interaction with the protein backbone. SAR development resulted in novel NS5B polymerase inhibitors exemplified by II (NS5B IC_{50} = 0.017 mM, replicon EC_{50} = 0.3 mM) with improved enzyme and replicon activity.



MEDI 102

Structure-based drug design and the evaluation of irreversible HCV-protease inhibitors

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Inhibitors of HCV NS3 protease have proven to have significant therapeutic benefit in clinical trials. However, the class as a whole suffers from the rapid emergence of drug resistant variants, and the effectiveness of current agents is limited to specific HCV genotypes. Moreover, achieving selectivity over host proteases remains a considerable challenge. Using structure-based drug design, we identified a class of small molecules that irreversibly bond to a non-catalytic amino acid residue, cysteine 159, in NS3 protease. This approach significantly improved inhibitor potency against the viral proteases and also achieved exceptional selectivity due to the lack of structural homology between viral and host proteases. More importantly, the covalent inhibitor showed prolonged duration of action (>24 hours) after brief exposure. In this presentation, we will report the SAR of our HCV NS3 irreversible inhibitors, together with *in silico* assessment of selected Michael acceptors.

MEDI 103

Synthesis and evaluation of novel biotin conjugated lipid prodrugs of cyclic cidofovir

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Cidofovir (HPMPC), an acyclic phosphonate nucleotide analogue of cytosine shows potential antiviral activity against herpes-, adeno-, polyoma- and poxviruses. It is currently used for treatment of AIDS-related cytomegalovirus retinitis. Cyclic cidofovir

(cHPMPC) displays less nephrotoxicity compared to HPMPC with higher antiviral potency. The major drawback with HPMPC/cHPMPC is their low oral bioavailability and poor transport across virus infected cells which limit therapeutic efficacy. With an aim to obtain targeted drug delivery and enhance lipid mediated cellular permeability here in we have evaluated novel transporter targeted lipid prodrugs of cyclic cidofovir. Targeted lipid prodrugs were synthesized by conjugating lipid rafts at one end of the cyclic cidofovir and tether the other end of these conjugates with biotin ligand for targeting sodium-dependent multivitamin transporter. Bifunctional lipid rafts containing 6 and 12 carbon chains were selected with two different functional groups (-OH and -NH₂) for linking one end to cyclic cidofovir and other end to biotin. To delineate the individual effects of targeting ligand and lipid raft on the prodrug properties, we have also synthesized and performed studies with Biotin- cHPMPC and Lipid (C6 and C12) - cHPMPC individually. All synthesized prodrugs were characterized by LC-MS/MS, ¹H NMR and ¹³C NMR and were evaluated with respect to their physicochemical properties i.e., aqueous stability, solubility, octanol/water partition coefficient and cytotoxicity.

MEDI 104

Preparing new betulinic acid derivatives for fighting HIV viruses

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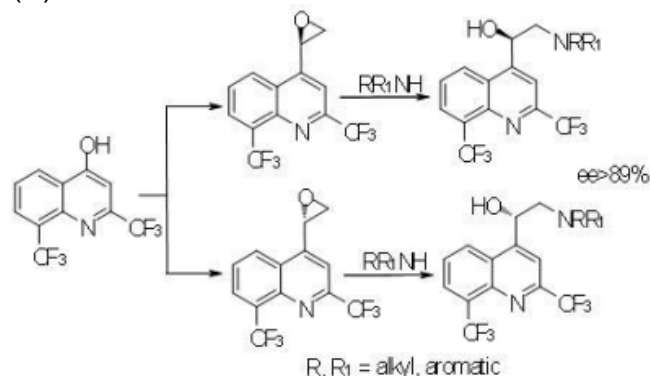
Betulinic acid is a naturally occurring pentacyclic triterpenoid that has several important biological activities including the inhibition of HIV viruses. This compound can be found in many plants such as birch bark. This compound has low toxicity due to its natural origin, but its application has been hampered by its low solubility in water and organic solvents. Therefore, many derivatives of betulinic acid have been synthesized to improve its biological functions including serving as potent and highly selective inhibitors of HIV-1. In this study, we have prepared derivatives of betulinic acid by conjugating it with an amino acid, followed by complexing the conjugate with organic cations to form ionic salts. We hypothesize the incorporation of an amino acid and the formation of an ionic compound will greatly improve the solubility of betulinic acid in water and organic solvents, which will then enhance the anti-HIV activity of betulinic acid. After the preparation of novel ionic salts of betulinic acid, the derivatives were evaluated for inhibiting the activities of HIV-1 protease. HIV-1 protease is a retroviral aspartyl protease that is essential to the maturation of HIV viruses, and thus the inhibition of protease disrupts the HIV's ability to replicate and infect additional cells. Using the HIV-1 protease-catalyzed peptide hydrolysis assay as monitored by the HPLC analysis, we have achieved some preliminary successes, which suggest that new ionic derivatives of betulinic acid are more inhibitory to the HIV-1 protease activity than betulinic acid itself.

MEDI 105

Synthesis of enantiopure antimalarial 4-aminoquinolinols

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Malaria is caused by *Plasmodium* and is responsible for 800.000 deaths in 2009. Research of new antimalarial chemotherapy has become urgent because of parasite resistance to classical drugs. Herein, we describe an enantiopure way to prepare enantiomeric 4-aminoquinolinols derivatives. A regioselective S_N2 ring opening of the epoxide, by diverse amines, allows us to obtain the corresponding (*R*) or (*S*) 4-aminoquinolinol with good yields and enantiomeric excesses generally above 89%. The (*S*)-enantiomers showed the best antimalarial activity.



MEDI 106

Efficient synthesis of amino-protected calix[4]arenes selectively functionalized with iron chelator ICL670 designed as platform for iron recognition

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Development of new tools to enable the selective detection of specific ions, ideally *in situ*, is a very ambitious challenge. For the specific medicinal applications, the developed ion sensors should be ideally integrated in miniaturized systems. For such a case, electrochemical detection is one of the simplest and cheapest types of measurements, and more specifically the potentiometric detection. Fe^{3+} is a major transition metal for all organisms and is an essential element for the critical steps of the cellular metabolism. Very few Fe^{3+} sensors have been reported so far and thus sensing and quantification of Fe^{3+} is still a challenging task. One promising possibility, to develop

ion sensors, is to use organically functionalized inorganic particles, for instance silica, as sensitive element. Herein, we present the design and synthesis of calix[4]arene-based platforms modified with ICL670 iron chelator and alkylamino chain(s). The formation of hybrid material and the first potentiometric test will be discussed.

MEDI 107

Synthesis of 4-thiouracil KPGEPGPK analogs as TIIICBP identification tools

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In a previous work, the identification of a new receptor for type III collagen named Type III Collagen Binding Protein (TIIICBP) has been reported. This receptor which is not yet identified is supposed to interact with the octapeptide sequence KPGEPGPK located in the $\alpha 1$ -chain of CB4 fragment of the type III collagen. Actually, the TIIICBP structure and the mechanisms of its corresponding interactions with KPGEPGPK are so far unknown. In this work, we described the synthesis of three octapeptides analogues that could be able to bind by a covalent way to the receptor TIIICBP via the use of 4-thiouracil probe. This probe has been incorporated at the 1 and/or 3 positions in KPGEPGPK sequence since it has been demonstrated that those positions could be mutated without major anti-thrombotic activity modifications. These analogues could be used to identify TIIICBP.

MEDI 108

Bacterial iron's uptake: A promising solution against multidrug resistant bacteria

Sylvain Fardeau¹, *sylvain.fardeau@u-picardie.fr*; Catherine Demailly-Mullie¹; Alexandra Dassonville-Klimpt¹; Nicolas Audic²; Pascal Sonnet¹. (1) Department of THERA, UMR-CNRS 6219, Amiens Picardie 80037, France (2) Pharmamens, Amiens Picardie 80037, France

It has been notified the strengthening of bacterial efflux system and the decreased permeability of bacterial membranes toward antibiotics. These phenomena have enabled the rise of multi-drug resistant bacteria. Besides micro-organisms need for their development iron, so they synthesize molecules called siderophores which bind extracellular ferric iron and transport it into themselves. Interestingly some micro-organisms have developed ingenious bacteriostatic agent: a bioactive molecule is linked with a siderophore-like fragment. This "Trojan Horse"'s strategy is based upon the specific recognition by the bacteria receptors and the absorption allows to bypass bacterial membranes and heightens the antibacterial activity. To develop new therapeutic agents against multi-drug resistant bacteria, we decided to work on siderophore-linked antibiotics: an iron (III) chelator linked by a cleavable chemical bond to a therapeutic agent. We reported here the synthesis and biological results of

catecholamides functionalized multi-amine backbone linked *via* a cleavable bond to a bioactive agent.

MEDI 109

Synthesis and evaluation of dual-action hybrid antimicrobials and prodrugs

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Clinical antibiotic resistance is often mediated via bacterial multi-drug resistance (MDR) efflux pumps. One strategy being explored for countering such resistance is to coadminister antibiotics with one or more MDR inhibitors; a strategy that is known to be used by plants to resist pathogens. Conceptually the approach is attractive for use in humans but in practice it is difficult to achieve therapeutic concentrations of two structurally unrelated compounds at target infection sites. In addition, the road to regulatory approval is vastly more complex for combination treatments than for single agents making this strategy unattractive from a development perspective. In efforts to address these shortcomings we've shown that non-cleavable dual-action hybrid compounds, comprising an antibacterial (berberine) linked to an MDR inhibitor (INF55), are effective antimicrobials against MDR-overexpressing bacterial cells. The presentation will summarise the synthesis and evaluation of several hybrids and describe our recent efforts towards antibacterial-MDR inhibitor prodrugs.

MEDI 110

Design, synthesis, and biological evaluation of novel Mtb-specific Dxr inhibitors as potential antitubercular agents

Geraldine San Jose¹, *gsanjose@gwu.edu*; **Kylene Kehn-Hall**²; **Helena I Boshoff**³; **Fatah Kashanchi**²; **Cynthia S Dowd**¹. (1) Department of Chemistry, George Washington University, Washington DC 20052, United States (2) Department of Molecular and Microbiology, George Mason University, Manassas VA 20110, United States (3) National Institute of Allergy and Infectious Diseases, National Institute of Health, Bethesda MD 20892, United States

Tuberculosis (TB), a highly contagious disease caused by *Mycobacterium tuberculosis* (Mtb), represents one of the most threatening health problems globally. The emergence of drug-resistant strains is a serious threat to TB control and treatment. There is an urgent need for the discovery and development of novel anti-tubercular agents. Mtb synthesizes isoprenoids, essential for mycobacterial survival, via the nonmevalonate pathway; the second step being mediated by the enzyme Dxr. Inhibitors of Dxr are

potential anti-TB agents. The nonmevalonate pathway is absent in humans, therefore, Dxr can be specifically targeted without interfering with human metabolism. The goal of this project is to design, synthesize and evaluate a unique class of analogues of fosmidomycin and FR900098, known inhibitors of Dxr, in order to study their structure-activity relationships and develop a new series of anti-TB drugs. Computational docking, synthetic results and biological evaluation will be presented.

MEDI 111

Identification and optimization of (E)-1-((2-(1-methyl-1H-imidazol-5-yl) quinolin-4-yl) methylene) semithiocarbazonates as a novel series of I κ B kinase β (IKK β) inhibitors

Youngsook Shin¹, yshin@amgen.com; Timothy D. Cushing¹; Vijay Baichwa²; Karen Berry³; Roland Billedeau⁴; Viola Bordunov⁵; Chris Broka⁴; Mario Cardozo⁶; Peng Cheng¹; David Clark¹; Stacie Dalrymple⁵; Michael DeGraffenreid¹; Adrian Gill⁴; Xiaolin Hao¹; Ronald C. Hawley⁴; Xiao He¹; Juan Jaen¹; Sharada S. Labadie⁴; Marc Labelle¹; Csaba Lehe²; Pu-Ping Lu¹; Joel McIntosh⁴; Shichang Miao³; Camran Parast²; Eric Sjogren⁴; Marie-Louise Smith¹; Francisco X. Talamas⁴; George Tonn³; Keith Walker⁴; Nigel P. C. Walker⁶; Holger Wesche²; Chris Whitehead⁴; Matt Wright³; Michelle Browner⁵. (1) Department of Chemistry, Amgen Inc., South San Francisco CA 94080, United States (2) Department of Molecular Biology, Amgen Inc., South San Francisco CA 94080, United States (3) Department of PKDM, Amgen Inc., South San Francisco CA 94080, United States (4) Department of Chemistry, Roche, Palo Alto CA 94304, United States (5) Department of Biology, Roche, Palo Alto CA 94304, United States (6) Department of Structural Biology, Amgen Inc., South San Francisco CA 94080, United States

Nuclear factor κ B (NF- κ B) plays a role in the regulation of inflammatory and immune responses, and control of cell division and apoptosis. I κ B kinase β (IKK β) has been identified as a potential target for the treatment of inflammatory and autoimmune diseases because of its role in the NF- κ B signaling pathway. We have developed a novel series of (E)-1-((2-(1-methyl-1H-imidazol-5-yl) quinolin-4-yl) methylene) semithiocarbazonates as potent inhibitors of IKK β . In this poster we document our early SAR efforts at optimization of the quinoline core, the imidazole moiety, and semithiocarbazone. The SAR around these groups was limited and most potency gains were obtained by substitution around the 6 and 7-positions of the quinoline ring. Replacement of the semithiocarbazone with a semicarbazone decreased the potency but increased the solubility leading to some measurable pharmacokinetics parameters.

MEDI 112

Novel series of I κ B kinase β (IKK β) inhibitors part II: Description of a potent and pharmacologically active series of analogs

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The highly homologous IKK β and IKK α are members of a small class of protein kinases known as I κ B kinase (IKKs). IKK β and IKK α activity are required for the activation of the transcription factor Nuclear factor κ B (NF- κ B). NF- κ B controls much of the innate immune system and is instrumental in the induction of genes leading to a pro-inflammatory response. Aberrant activation of the NF- κ B pathway has been implicated in inflammation, autoimmune diseases and cancer. Drugs targeting these kinases are very promising candidates for the treatment of many diseases. A Novel series of (E)-1-((2-(1-methyl-1H-imidazol-5-yl) quinolin-4-yl) methylene) thiosemicarbazides was discovered as potent inhibitors of IKK β . In this poster we document our efforts at further optimization of this series, culminating in compound 2 which exhibited submicromolar activity in a HWB assay and efficacy in a CIA mouse model.

MEDI 113

Benzothiadiazoles as MAPKAP kinase 2 inhibitors

Jennifer Thomason, jennifer.thomason@pfizer.com; Kerry Combs; Bruce Follows; Steve Kirincich; WeiHeng Wang; Jean-Baptiste Telliez; Julie Liu; Ariamala Gopalsamy; Lynn Resnick; Frank Lovering. Department of Inflammation and Immunology, Pfizer, Cambridge MA 02140, United States

MK2 (Mitogen Activated Protein Kinase Activated Protein Kinase 2) is a Serine/Threonine kinase regulated by phosphorylation by p38 MAP kinase. Activation occurs during the inflammation response where MK2 regulates the biosynthesis of TNF α , a cytokine that plays a significant role in a number of inflammatory disease states including rheumatoid arthritis. The link between MK2 and TNF α has been established from the MK2 knockout study. The -/- MK2 mice have reduced LPS mediated TNF α production, are resistant to LPS/D-Gal induced shock and are otherwise healthy. MK2 knockout mice are also resistant to collagen induced arthritis. Compounds that inhibit MK2, therefore, could potentially be useful in the treatment of many TNF α mediated

diseases such as rheumatoid arthritis. The development of a class of novel MK2 inhibitors containing a thiadiazole core will be discussed.

MEDI 114

Delivery of inhaled corticosteroid (ICS) and long acting beta agonist (LABA) via mutual prodrug strategy for the treatment of pulmonary inflammation and bronchoconstriction

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Combination therapy of ICS and LABA is a frontline treatment for asthma and COPD patients. We will present the design and synthesis of a novel linking strategy to deliver an ICS and LABA from a single chemical entity that is unmasked to the individual components by a metabolic process. Data will be presented illustrating improved PK and safety in animal models over the individual components.

MEDI 115

Discovery of 4,5-dihydroindazole-based dissociated agonists of glucocorticoid receptor

Zhonghui Lu, *zhonghui.lu@bms.com; James J.-W. Duan; Bin Jiang; David S. Weinstein; Hua Gong; Arthur M. Doweiko; Christine Burke; Sium Habte; Jinhong Wang; Ding Shen; Lorraine McKay; John E. Somerville; Steven G. Nadler; John Dodd; Joel C. Barrish. Discovery Chemistry, Bristol-Myers Squibb Company, Princeton NJ 08543, United States*

Synthetic glucocorticoids (GCs) such as dexamethasone, prednisolone and cortivazol are among the most effective agents for the treatment of autoimmune and inflammatory diseases. Their long-term administration is often complicated by a number of side-effects which limit broader indication of this class of drugs. Therefore identification of glucocorticoid receptor (GR) ligands which maintain the anti-inflammatory and immunosuppressive activity of GCs while minimizing side-effects has attracted significant interest in the pharmaceutical industry. 4,5-Dihydroindazoles represent a structurally simplified chemical series of GR agonists relative to steroidal ligands. The synthesis and SAR of these modulators will be described in detail.

MEDI 116

Discovery of 2-aryl-5H-chromeno[2,3-b]pyridines (azaxanthenes) as selective glucocorticoid receptor modulators

Hua Gong, *hua.gong@bms.com*; David S. Weinstein; Arthur M. Doweyko; Jinhong Wang; Mark Cunningham; Deborah Holloway; Sium Habte; Christine Burke; David Shuster; Luisa Saltercid; Ling Gao; Julie Carman; John Dodd; John E. Somerville; Steven G. Nadler; Joel C. Barrish. *Research and Development, Bristol-Myers Squibb Company, Princeton NJ 08543, United States*

There has been intense interest in the identification of selective GR modulators (SGRMs) which maintain the anti-inflammatory and immunosuppressive efficacy of steroidal glucocorticoid ligands with a reduced side effect profile. In this presentation structure-activity relationship (SAR) for a series of selective GR ligands based on the 5*H*-chromeno[2,3-*b*]pyridine (azaxanthene) scaffold will be described. It was found that *para*-substituted phenyl on the *S*-enantiomer of the azaxanthene core provides varying levels of GR agonist activity. These azaxanthene ligands are pharmacologically characterized as competitive partial agonists/partial antagonists of GR transactivation. A structural model for ligand binding is also presented. Antiinflammatory efficacy in rats of selective compounds in this series and synthesis of the azaxanthenes will also be discussed.

MEDI 117

Novel agonists and antagonists for protease activated receptor 2

Annika M. Yau, *a.yau@imb.uq.edu.au*; Ligong Liu; Robert C Reid; Grant D Barry; Jacky Y Suen; Rink-Jan Lohman; Giang T Le; Adam Cotterell; David P Fairlie. *Division of Chemistry and Structural Biology, Institute for Molecular Bioscience, Brisbane Queensland 4072, Australia*

Protease activated receptor 2 (PAR2) is a class A G protein-coupled receptor that is expressed on the surface of many types of cells. The roles of PAR2, as implicated in a number of diseases including inflammatory disorders, cancers, cardiovascular diseases and asthma, make it a potential new drug target. The mechanism of activation of PAR2 is unique. Unlike other GPCRs, PAR2 has no known endogenous ligand. Instead the N-terminus of the receptor is cleaved by serine proteases (e.g. trypsin, tryptase but not thrombin) at a specific site, and is self-activated through binding of the newly exposed N-terminus (also known as a tethered-ligand, TL) to the receptor. Synthetic peptides corresponding to TL can also activate PAR2 and are used to characterize physiological roles of PAR2. However these peptides have low potency (e.g. SLIGKV-NH₂, SLIGRL-NH₂), uncertain target selectivity and poor bioavailability, which limit their usefulness for specifically interrogating PAR2 *in vivo*. In our drug discovery program, we successfully developed potent, selective, non-peptidic PAR2 agonists and antagonists, evaluated in both *in vitro* and *in vivo* studies. Some of these compounds and activities will be described. References: 1) Barry, G. D.; Suen, J. Y.; Le, G. T.; Cotterell, A.; Reid, R. C.; Fairlie, D. P. *J. Med. Chem.* **2010**, 53, 7428. 2) Adams, M. N.; Ramachandran, R.; Yau, M. K.; Suen, J. Y.; Fairlie, D. P.; Hollenberg, M. D.; Hooper, J. D. *Pharmacol. Ther.* **2011**, *in press*. DOI: 10.1016/j.pharmthera.2011.01.003.

MEDI 118

SAR studies on peptide agonists of proteinase activated receptor-2 (PAR-2)

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PAR-2 is a GPCR that has been implicated in the pathophysiology of diseases such as rheumatoid arthritis, inflammatory bowel diseases and multiple sclerosis. Human PAR-2 is activated by cleavage by a serine protease (e.g. Trypsin), thereby revealing the N-terminal peptide SLIGKV, which in turn intramolecularly binds and activates the juxtamembrane region of the receptor. Structure/activity studies based on a related and potent PAR-2 peptide agonist 2-furoyl-LIGRLO-NH₂ will be presented. The results of those studies, in addition to NMR experiments, CD analysis and modeling techniques, were used to determine the presence and identity of the peptide's secondary structure. PAR-2 macrocycles that mimic this structure were synthesized and will also be reported.

MEDI 119

Design, synthesis, and structure-activity relationship studies of novel, potent and orally bioavailable CRTH2 antagonists

Tadashi Terasaka¹, tadashi.terasaka@jp.astellas.com; Hisashi Hayashida²; Hiroshi Matsuda²; Junji Miyata¹; Hiroshi Nagata²; Shinji Ito¹; Yuji Takasuna¹; Miki Kobayashi¹; Makoto Takeuchi¹; Mitsuaki Ohta¹. (1) Drug Discovery Research, Astellas Pharma Inc., 21, Miyukigaoka, Tsukuba Ibaraki 305-8585, Japan (2) Astellas Research Technologies Co., Ltd., 21, Miyukigaoka, Tsukuba Ibaraki 305-8585, Japan

A recent report from our laboratories described the discovery of novel, potent and orally bioavailable CRTH2 antagonist, **2** (IC₅₀ = 13 nM to human CRTH2) based on the initial optimization of lead compound **1** (IC₅₀ = 42 nM) discovered from high throughput screening of our chemical library. Although compound **2** was designed by

William Nguyen¹, william.nguyen@monash.edu; Heike Wulff²; Brittany Howard¹; Paul White¹; Philip Thompson¹; David Manallack¹. (1) Medicinal Chemistry & Drug Action, Monashi University, Australia (2) University of California, United States

Psoriasis is an autoimmune disorder of the skin that affects millions of people worldwide. Current treatments have limitations concerning their efficacy, side effect profiles and cost. The need for better treatments is clear and our research is aimed at developing a novel therapy for psoriasis with an improved profile. Previous research has shown that a drug normally used for diarrhoea (diphenoxylate) was able to treat psoriasis; however this important observation was not fully evaluated. Our preliminary work has demonstrated that diphenoxylate blocks a key potassium channel (Kv1.3) associated with the immune system. Indeed, Kv1.3 channels have been shown to have a role in autoimmune disorders such as psoriasis and may explain the observations that diphenoxylate was able to treat psoriasis. Our initial research has generated novel analogues of diphenoxylate to explore the SAR of this molecule at Kv1.3 channels. Further synthetic work has built on this initial SAR to generate compounds that are over 100 times more potent at Kv1.3 channels than our original lead, diphenoxylate. In addition these potent Kv1.3 blockers are lower in molecular weight and have reduced lipophilicity. These interesting leads will be assayed in functional tests to assess their antiproliferative activity.

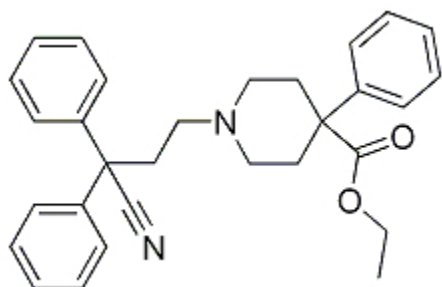


Fig 1. Diphenoxylate

MEDI 122

Na,K-ATPase $\alpha 4$ as a target for male contraception

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Four isoforms of the Na,K-ATPase catalytic subunit ($\alpha 1$ -4), a plasma membrane-bound enzyme responsible for maintaining the transmembrane Na^+ and K^+ gradients, have been described in mammals. The $\alpha 4$ isoform is expressed specifically in the male germ cells of the testis and is essential for sperm motility. The natural cardenolide ouabain is a potent and selective inhibitor of Na,K-ATPase $\alpha 4$ (K_i 7 nM) over the ubiquitous $\alpha 1$ isoform (K_i 43,000 nM). We built a homology model of human Na,K-ATPase $\alpha 4$ based on the co-crystal structure of shark Na,K-ATPase $\alpha 1$ in its ouabain-bound state. To identify new structures selective toward Na,K-ATPase $\alpha 4$, we performed a high throughput virtual screen of a library containing 230K compounds. A number of

commercially available drugs were identified as possible inhibitors of the enzyme, including antihistamines. Following further docking studies, one compound was selected for in vitro analysis and shown to inhibit rat sperm motility.

MEDI 123

Characterization of the benzene sulfonic acid salt form of VA111913 as a potential clinical development candidate for the treatment of dysmenorrhea

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Dysmenorrhea (painful menstrual cramps) is a common gynecological condition occurring in more than 50% of menstruating women. These women have increased uterine muscle tone and contractions and decreased blood flow to the uterus. This leads to the pain experienced in dysmenorrhea. The hormone vasopressin, via the V1a receptor, induces contractions in both uterine smooth muscle and uterine blood vessels. A V1a receptor antagonist will potentially inhibit these contractions and in turn reduce the pain experienced in dysmenorrhea. VA111913 is such an antagonist whose structure and properties have been previously disclosed (239th ACS National Meeting, San Francisco, CA, March 21-25 2010). A benzene sulfonic acid salt of VA111913 has been identified that confers significant advantages over the free base. It has enhanced solubility in water and shows good exposure after oral administration to rats. Its preparation, physico-chemical properties and pharmacokinetics will be presented. This salt form is suitable for clinical development.

MEDI 124

T3P[®]: The green reagent of choice for condensation reactions

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n-Propane Phosphonic Acid Cyclic Anhydride (T3P[®]) is an exceptional reagent for amide/peptide bond formation. Further, recent research has extended the application of this reagent to other condensation reactions, such as esterifications, and formation of both isonitriles and nitriles. In addition, T3P[®] has found utility as a mild reagent for alcohol oxidations and the Lossen rearrangement. T3P[®] is very easy to use and provides excellent selectivity, low epimerization and high yields with simple product isolation by liquid/liquid extraction. Because of its properties, hazardous additives such as explosive HOBt, are not required. Additionally, the T3P[®] reagent is really “green” - nontoxic, non-allergenic/non-sensitizing, and the salt by-products are non hazardous and completely water soluble, in sharp contrast to most other coupling reagents. These salts are readily removed via an aqueous wash at the conclusion of the reaction.

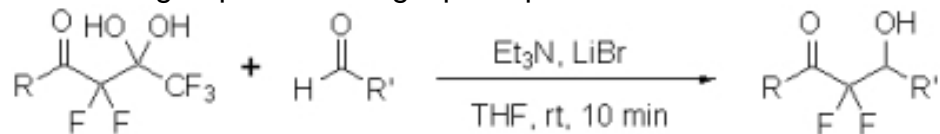
Numerous examples of the condensation reactions will be presented, wherein the inherent advantages of T3P[®] will be highlighted.

MEDI 125

Cleavage of carbon-carbon bonds through the mild release of trifluoroacetate towards mono-, and difluorinated compounds

Eun Hoo Kim¹, ehkim@purdue.edu; David A. Colby^{1,2}. (1) Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, West Lafayette IN 47907, United States (2) Department of Chemistry, Purdue University, West Lafayette IN 47907, United States

Fluorinated compounds are of great interest in medicinal chemistry due to their biological activities, and subsequently, have attracted the attention of many synthetic chemists. In order to install fluorinated functional groups on complex molecules. A method to generate reactive fluorinated intermediates has been discovered using the facile release of trifluoroacetate. The application of this process to substrates bearing ketones, phosphonates, and sulfones as stabilizing groups is presented to efficiently synthesize mono- and difluorinated products. Also, this synthetic method is effectively applied to complex chiral substrates to include fluorine without affecting sensitive functional groups or causing alpha-epimerization.



MEDI 126

WITHDRAWN

MEDI 127

Lead generation using a privileged structure-based approach

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The *privileged structure-based* approach is considered a reliable route to lead generation. Privileged structures are substructures capable of providing high affinity ligands for more than one biological target. The present study involves the synthesis of a library using 2-aminothiazole as the core structure. Bioactive fragments shown to produce hits in a variety of biological targets were incorporated on the 2-aminothiazole scaffold. Synthetic routes to the *privileged structure-based* compounds were developed

using microwave and thermal conditions. Sulfonamidation afforded sulfonamide based compounds while Suzuki coupling of the scaffold with an array of boronic acids resulted in Suzuki products which were further elaborated by coupling with beta lactam and lactone fragments. The library was tested in a variety of biological assays (antimicrobial, and as modulators of muscarinic, serotonin receptors and glutamate transporter [GLT-1]). Data pertaining to those assays and lead molecules that have been identified will be presented and discussed.

MEDI 128

TIDEA in-silico screening enhances potency, ligand efficiency, and drug-like nature while maintaining chemical diversity

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TIDEA (Target-Independent Drug Enhancement Algorithm) is software for in-silico screening of bioactive low-FW ligands that selects more potent ligands without knowledge of the target structure or ligand SAR. TIDEA determines a degree of adhesiveness that is independent of the specific ligand/target shape complementarity. TIDEA has the advantage over conventional methods (rational design, QSAR) of maintaining the molecular shape diversity of the original ligand set, making it ideal as a filter to improve potency in universal libraries intended for screening against multiple targets. Even when every molecule in the test set has a different target, subsets with high TIDEA scores (>9.5) show higher average potencies and enrichment of potent ($<100\text{nM}$) ligands with statistical significance ($p<0.03$). TIDEA also distinguishes drug-like from non-druglike molecules, with a statistical significance of $p<0.0001$. A modification optimized for fragment-based lead discovery, TIDEA/FBLD, selects for small molecules with higher ligand efficiency.

MEDI 129

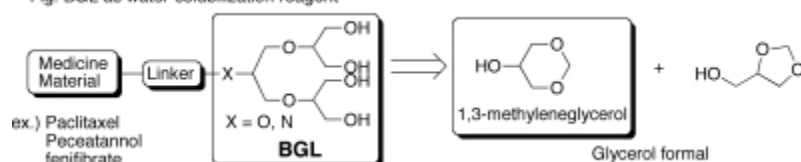
Efficient and practical method for the preparation of branched oligoglycerols (BGL) from 1,3-methyleneglycerol for water-solubilization of medicinal compounds

Hatsuhiko Hattori, *hhattori@ph.tokushima-u.ac.jp*; Kohsuke Yoshitomi; Ayato Katagiri; Tsuyoshi Matsushita; Masaki Kamiya; Keisuke Ishizawa; Koichiro Tsuchiya; Hisao Nemoto. Institute of Health Bioscience, The University of Tokushima, Tokushima Tokushima 770-8505, Japan

Recent improvements of high throughput screening techniques have ironically brought into a number of poorly water-soluble medicinal candidates, which have been often dropped out due to the poor water-solubility. Our developed branched oligoglycerols (BGL) is a chemically pure single molecule without asymmetric center to be suitable for water-solubilizing of such a shelved candidate. In this paper, we report a method for

practical large-scale preparation of BGL from 1,3-methyleneglycerol.

Fig. BGL as water-solubilization reagent



MEDI 130

Surface modification procedure of acellular vascular grafts with the cell binding peptide

Atsushi Mahara, mahara@ri.ncvc.go.jp; Naoto Mihashi; Jeong-Hun Kang; Tetsuji Yamaoka. Department of Biomedical Engineering, National Cerebral and Cardiovascular Center Research Institute, Suita Osaka 5658565, Japan

Decellularized tissue has a potential as ideal scaffold to regenerative medicine, because of the structural similarity to the native tissue. We have employed the ultrahigh-hydrostatic pressure (UHP) (1000MPa) as a decellularization technology. In the previous study, good anti-thrombogenic and mechanically stable properties of the decellularized porcine aorta were confirmed after the transplantation for up to 1 year. Nevertheless, calcification on the decellularized tissue was found in rare case. To prevent the calcification on the graft, we have developed the surface modification procedure of acellular vascular grafts with cell binding peptide. Synthetic peptides containing collagen binding domain and cell binding domain were prepared. Binding affinity of endothelial cells on the peptide-modified decellularized tissue was observed in peptide sequence specific manner in vitro. Moreover, the peptide-modified acellular rat aortas were implanted into rats, and the patency and tissue regeneration were evaluated.

MEDI 131

Quantification of total ω -6, total ω -3 and ω -6/ ω -3 ratio in human serum using GC/MS

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Quantitative determination of polyunsaturated fatty acids (PUFAs) in human serum has been of great challenge to researchers today. The work in this study has quantified six PUFA methyl esters, three which are the (ω -6) esters of linoleic (LAME), conjugated linoleic (CLAME) and arachidonic (AAME) and three others that are the (ω -3) esters of linoleic (LNAME), eicosapentaenoic (EPAME), and docosahexaenoic (DHAME)) fatty acids using GC/MS. Blood serum aliquots taken from the same subjects were analyzed on the same day using GC/MS and visible spectrophotometric detections. Data obtained from GC/MS were quantified according to protocol. Spectral absorbance data

from 350-550nm were analyzed using chemometric model, PLS2. Results obtained from the two methods were correlated using student t-test and resulted in good agreements between total (ω -3) and total (ω -6) PUFA levels and for the (ω -6)/ (ω -3) ratios $\alpha=0.05$, $t_{cal}=-0.59$, $t_{cri}=2.18$, $P=0.57$. The greatest achievement of this study is that, the study was able to apply the separation method described to blood serum for the quantification of total ω -6, total ω -3 and ω -6 to ω -3 ratios using GC/MS for the first time therefore improving the GC separation and detection an aspect that is of great importance to chromatographers and medical line.

MEDI 132

Synthesis and hydrolytic properties of thymidine *P*-boranomonophosphate

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Structure modification of nucleoside analogs with the isoelectronic substitution of borane (BH₃) group for one of the nonbridging oxygens in phosphate esters increases the lipophilicity and other properties of the phosphate in nucleotides, DNA and RNA. A general synthesis for nucleoside *P*-boranomonophosphates by H-phosphonates used in our group was briefly discussed in the recent review by our group (Li et al, *Chem. Rev.*, 2007). Here we report the H-phosphonate approach to obtain thymidine 5'-*P*-boranomonophosphate in a more convenient and detailed procedure. The reactions were monitored by ³¹P-NMR and identified by spectral data. Hydrolysis studies of thymidine *P*-boranomonophosphate by LC-MS were carried out in buffers of different pH and temperature. As predicted, more acidic conditions considerably increased the hydrolysis rate. At 22 °C and 37 °C, a seven-fold difference in rates was observed. Based on our study, we suggest that nucleoside boranomonophosphates should be kept in dry form at low temperature.

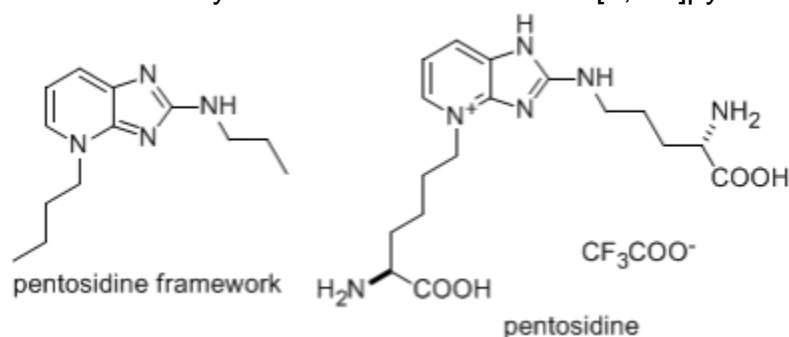
MEDI 133

Synthesis of pentosidine framework

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Pentosidine is a fluorescent advanced glycation endproduct that serves as a biomarker of diabetic complications, kidney dysfunction, oxidative stress, as well as aging and age-related diseases. Pentosidine framework, 4-butyl-2-propyl-4*H*-aminoimidazo[4,5-*b*]pyridine, was synthesized through a five steps reaction sequence including regioselective alkylation of 2-(methylthio)imidazo[4,5-*b*]pyridine, chlorination of methylthio group, and amination of 2-chloro-imidazo[4,5-*b*]pyridine. This method is of material accessibility and operational simplicity and also serves as a general method to

construct 4-alkylated-2-amino-4*H*-imidazo[4,5-*b*]pyridines.



MEDI 134

Phenylalanine derivatives as GPR142 agonists for treatment of type II diabetes

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GPR142 is a novel GPCR which is predominantly expressed in pancreatic b-cells. GPR142 agonists potentiate glucose-sensitive insulin secretion in a GPR142-dependent manner from isolated pancreatic islets and in rodent models. We are interested in developing small molecule GPR142 agonists to treat type II diabetes. Optimization of the SAR of our lead amrinone-phenylalanine series resulted in compound **20**, which demonstrated glucose-lowering effect in a mouse model. Further optimization led to the thiadiazole B ring series which had improved PK and CYP inhibition profile.

MEDI 135

Amino-pyrazole phenylalanine GPR142 agonists for the treatment of type II diabetes

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GPR142 is a GPCR highly expressed in islet beta-cells and is responsible for the endogenous ligand-mediated glucose-dependent secretion of insulin. Studies in rodent islets and in *in-vivo* models suggest that a suitable small molecule GPR142 agonist could be of benefit in the treatment of type II diabetes. This poster highlights our systematic lead optimization of the amrinone-phenylalanine series, which led to the identification of a novel pyrazole-based scaffold displaying desirable properties including high *in-vitro* activity, minimal CYP inhibitory activity and moderate to excellent systemic stability. Combination of the optimal features provided tool compound 30 and its pro-drug, which showed good efficacy in mouse oral glucose tolerance test (OGTT) studies.

MEDI 136

Design, evolution, and in vivo profile of a novel series of GPBAR 1 agonists for the treatment of diabetes and metabolic syndrome

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GPBAR1 (TGR5), a G protein coupled bile acid receptor, represents an important signaling pathway for regulating energy homeostasis and metabolic control. Activation of GPBAR1 stimulates cAMP production in both adipose tissue and enteroendocrine cells leading to an increase in mitochondrial function and GLP-1 secretion in the respective tissues. Herein, we report our efforts on GPBAR1 receptor agonists that led to the discovery of a potent series of heterocyclic linked di-aryl compounds with balanced activity on both human and mouse receptor. Lead optimization, SAR, *in vitro* potency and *in vivo* efficacy will be discussed.



MEDI 137

Discovery of 7-oxo-pyrrolopyridines as potent and selective inhibitors of DPP4

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Inhibitors of dipeptidyl peptidase 4 (DPP4), a member of the serine protease super-family, have attracted considerable attention as novel therapeutic agents for the treatment of diabetes mellitus. Sitagliptin (Januvia™) and Saxagliptin (Onglyza™) are the currently approved DPP4 inhibitors in the United States for the treatment of type 2 diabetes. This presentation describes the design, synthesis, and SAR of a novel class of 7-oxopyrrolopyridine-derived DPP4 inhibitors. The preferred stereochemistry of these atropisomeric biaryl analogs has been identified as Sa. A selective amide analog derived from this series, with a DPP4 K_i of 0.37 nM, showed a significant improvement in insulin response in *ob/ob* mice.

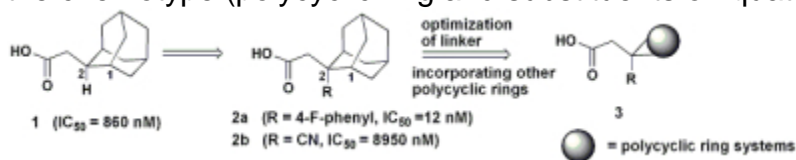
MEDI 138

Design, synthesis, and SAR studies of novel polycyclic acids as potent and selective inhibitors of human 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD1)

Xiang-Yang Ye¹, xiang-yang.ye@bms.com; Stephanie Y Chen¹; Shung Wu¹; Akbar Nayeem²; David Yoon¹; Haixia Wang¹; Zhenqiu Hong¹; Steve O'Connor¹; Atsu Apedo³; James J Li¹; Jun Li¹; Rajasree Golla⁴; Ramakrishna Seethala⁴; Mengmeng Wang⁵; Timothy Harper⁵; Bogdan G Slecza³; David Gordon⁶; Jeffrey A Robl¹; Lawrence Kennedy¹; Steven Walker¹. (1) Metabolic Diseases Chemistry, Bristol-Myers Squibb Co., Princeton New Jersey 08543-5400, United States (2) CADD, Bristol-Myers Squibb Co., Princeton New Jersey 08543-5400, United States (3) DAS, Bristol-Myers Squibb Co., Princeton New Jersey 08543-5400, United States (4) Lead Evaluation, Bristol-Myers Squibb Co., Princeton New Jersey 08543-5400, United States (5) MAP, Bristol-Myers Squibb Co., Princeton New Jersey 08543-5400, United States (6) Department of Biology, Bristol-Myers Squibb Co., Princeton New Jersey 08543-5400, United States

Starting from high throughput screening hit 2-adamantyl acetic acid **1**, a series of polycyclic acids **3** have been designed and synthesized as novel, potent, and selective inhibitors of human 11b-HSD1. Structure-activity relationships of two different regions of

the chemotype (polycyclic ring and substituents on quaternary carbon) are discussed.

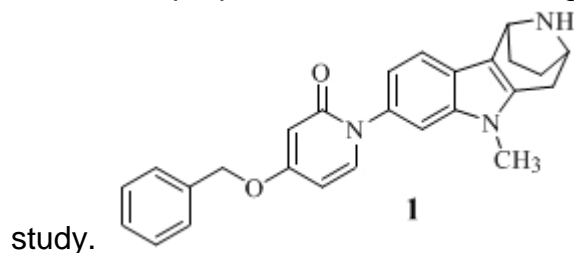


MEDI 139

Synthesis and SAR of 5-methyl-5,6,7,8,9,10-hexahydro-7,10-iminocyclohept[b]indoles and 5-methyl-6,7,8,9,10,11-hexahydro-7,11-imino-5H-cyclooct[b]indoles as MCH-1 receptor antagonists

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A new class of MCH-1 receptor antagonists, exemplified by compound **1**, was discovered and tested in a MCH-1 receptor binding assay. Selected enantiopure compounds were obtained by preparatory chiral HPLC and further evaluated for in vitro and in vivo properties, and showed weight loss in a 5-day diet-induced obese mouse



MEDI 140

Synthesis and in vivo evaluation of 6-(4-fluorophenoxy)-3-((1-[¹¹C]methylpiperidin-3-yl)methyl)-2-o-tolylquinazolin-4(3H)-one, a potential PET tracer for Growth Hormone Secretagogue receptor (GHSR)

Rachel A Potter, rpotter8@jhmi.edu; Andrew G Horti; Daniel Holt; Ursula Scheffel; Robert F Dannals; Richard L Wahl. Department of Radiology, Johns Hopkins University, School of Medicine, Baltimore Maryland 21205, United States

Since its initial discovery, ghrelin has been shown to play a fundamentally important role in diet induced obesity through its action on the ghrelin receptor (GHS-R) located in the hypothalamus. While an enormous amount of data highlights the presence of ghrelin in the CNS and its role in appetite stimulation, the exact mechanism of action is still largely unknown. Imaging the GHS-R receptor in the brain could offer better insight into the actual physiological pathways of how ghrelin regulates food intake and thus aid in

developing potent and more selective anti-obesity drugs. This study describes the synthesis, in vitro and in vivo evaluation of 6-(4-fluorophenoxy)-3-((1- ^{11}C)methylpiperidin-3-yl)methyl)-2-o-tolylquinazolin-4(3H)-one (^{11}C), a potential PET radioligand for imaging GHSR.

MEDI 141

Synthesis of PET TSPO radioligand [^{18}F]PBR06 using a new tosylated precursor

Min Wang, wang1@iupui.edu; Mingzhang Gao; Qi-Huang Zheng. Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis IN 46202, United States

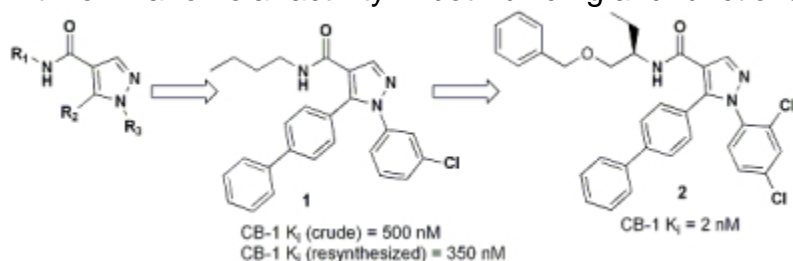
The translocator protein 18 kDa (TSPO), formerly known as peripheral-type benzodiazepine receptor (PBR), is an attractive target for molecular imaging of neuroinflammation and tumor progression. [^{18}F]PBR06 (*N*-(2,5-dimethoxybenzyl)-2- ^{18}F fluoro-*N*-(2-phenoxyphenyl)acetamide) is a promising PET brain TSPO radioligand originally developed by Briard et al at NIMH. Wishing to study this compound in our laboratory, we decided to make our own materials by following the literature methods. However, the published production of [^{18}F]PBR06 using the reaction of [^{18}F]fluoride ion with the corresponding bromo precursor resulted in low specific activity, radiochemical yield and chemical purity of [^{18}F]PBR06 in our hands, due to difficult separation of the F-18 labeled product from the precursor, and moderate leaving group bromo of the precursor. While studying the reported methods for [^{18}F]PBR06 production, we discovered a new labeling precursor, the previously undescribed tosylate congener of PBR06 with better leaving group tosyl, and investigated a fully automated synthesis of [^{18}F]PBR06. PBR06 (*N*-(2,5-dimethoxybenzyl)-2-fluoro-*N*-(2-phenoxyphenyl)acetamide) and its bromo precursor (2-bromo-*N*-(2,5-dimethoxybenzyl)-*N*-(2-phenoxyphenyl)acetamide) were synthesized from 2,5-dimethoxybenzaldehyde in 3 and 2 steps with 71% and 78% overall chemical yield, respectively, according to the literature methods. New tosylated precursor (2-((2,5-dimethoxybenzyl)(2-phenoxyphenyl)amino)-2-oxoethyl 4-methylbenzenesulfonate) was designed and synthesized from ethyl 2-hydroxyacetate, 4-methylbenzene-1-sulfonyl chloride, and *N*-(2,5-dimethoxybenzyl)-2-phenoxyaniline in 4 steps with 50% overall chemical yield. [^{18}F]PBR06 was prepared by the nucleophilic substitution of either new tosylated precursor or previously described bromo precursor in DMSO at 150 °C with $\text{K}^{18}\text{F}/\text{Kryptofix 2.2.2}$ for 15 min and HPLC combined with SPE purification in 20-60% decay corrected radiochemical yield from [^{18}F]fluoride at EOB, >99% radiochemical purity, 87-95% chemical purity, and 74-222 GBq/ μmol specific activity at EOB, in an home-built automated multipurpose ^{18}F -radiosynthesis module. The radiosynthesis of [^{18}F]PBR06 using new tosylated precursor gave similar radiochemical purity, and much higher specific activity, radiochemical yield and chemical purity in comparison with the bromo precursor.

MEDI 142

Discovery and optimization of 1,5-diarylpyrazole-4-carboxamides as novel CB-1 inverse agonists

Annapurna Pendri¹, annapurna.pendri@bms.com; Dharmpal S Dodd²; Zheming Ruan²; Jing Chen²; Mary Ellen Cvijic²; Rose A Baska²; Liya Kang²; Neil T Burford¹; Kenneth E Carlson²; William R Ewing²; Samuel W Gerritz¹. (1) Research and Development, Bristol-Myers Squibb, Wallingford CT 06492, United States (2) Research and Development, Bristol-Myers Squibb, Princeton NJ 08453, United States

As part of an effort to identify novel G-protein coupled receptor ligands, a 8000 member GPCR-targeted library of 1,5-diarylpyrazole-4-carboxamides was synthesized using a novel solid-phase synthesis. Screening of the library samples provided hits containing 5-biphenylpyrazole-4-carboxamide motif with promising activity against the cannabinoid receptor subtype 1 (CB-1). This presentation will describe the initial discovery and optimization of the hit series (i.e. **1** to **2**), resulting in the identification CB-1 antagonists with low nanomolar activity in both binding and functional assays



MEDI 143

Structural and mechanistic models of VKORC1

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VKORC1 is located in the ER membrane, and is the only enzyme capable of reducing vitamin K 2,3-epoxide, and is thus a critical enzyme in the vitamin K cycle. The enzyme is inhibited by warfarin, and the use of warfarin rodenticides for over 50 years has resulted in a wide range of mutations leading to warfarin resistance, and several inborn coagulation deficiencies are traced to SNPs in the VKORC1 gene. In this paper, we propose a model for the VKORC1 enzyme consisting of 4 transmembrane helices and one short helix in the ER lumen is proposed, along with a region consisting of β -strands. This model permits the effects of all known mutations on the activity of the enzyme and the binding of warfarin to be rationalized. The reduction of vitamin K 2,3-epoxide involves three cysteine residues.

MEDI 144

Discovery of small molecule P2Y₁ antagonists part I: Biaryl ureas

Hannguang J. Chao¹, Hannguang.chao@bms.com; Huji Turdi¹; Timothy F. Herpin¹; Jacques Y. Roberge¹; Yalei Liu¹; Dora Schnur²; Michael A. Poss¹; Robert Rehfuss³; Ji Hua³; Qimin Wu³; Luara A. Price³; Lynn Abel³; William A. Schumacher³; Jeffrey A. Bostwick³; Anne B. Stewart³; Martin L. Ogletree³; Ruth R. Wexler⁴; Patrick Y. S. Lam⁴; R. Michael Lawrence¹. (1) Early Discovery Chemistry, Bristol-Myers Squibb, Princeton NJ 08543-5400, United States (2) CADD, Bristol-Myers Squibb, Princeton NJ 8543-5400, United States (3) CV Biology, Bristol-Myers Squibb, Princeton NJ 8543-5400, United States (4) Medicinal Chemistry, Bristol-Myers Squibb, Princeton NJ 8543-5400, United States

Two distinct G protein-coupled purinergic receptors, P2Y₁ and P2Y₁₂, mediate ADP driven platelet activation. The clinical effectiveness of P2Y₁₂ blockade is well established. Recent preclinical data suggests that P2Y₁ and P2Y₁₂ inhibition provide equivalent antithrombotic efficacy, while targeting P2Y₁ has the potential for reduced bleeding liability. In this presentation, we will describe the discovery of a 2-(phenoxy pyridine)-3-(phenyl) urea chemotype that inhibited ADP-mediated platelet aggregation in human blood samples via high throughput screening. Further optimization of this series led to the identification of the lead compound 1-(2-(2-tert-butylphenoxy) pyridin-3-yl)-3-(4-(trifluoromethoxy) phenyl) urea which was shown to antagonize the P2Y₁ receptor, leading to an antithrombotic effect in a rat thrombosis model.

MEDI 145

Discovery of small molecule P2Y₁ antagonists part II: 2-aminothiazole based P2Y₁ antagonists as novel antiplatelet agents

Zulan Pi, zulan.pi@bms.com; James Sutton; John Lloyd; Robert Rehfuss; Ji Hua; Qimin Wu; Laura A. Price; Ruth R. Wexler; Patrick Y. S. Lam. Research and Development, Bristol-Myers Squibb Company, Princeton New Jersey 08543-5400, United States

Two distinct G protein-coupled purinergic receptors, P2Y₁ and P2Y₁₂, mediate ADP driven platelet activation. The clinical effectiveness of P2Y₁₂ blockade is well established. Recent preclinical data suggests that P2Y₁ and P2Y₁₂ inhibition provide equivalent antithrombotic efficacy, while targeting P2Y₁ has the potential for reduced bleeding liability. BMS previously identified a series of *t*-butylphenoxy pyridinyl urea analogs as small molecule P2Y₁ antagonists. This poster presents our efforts to employ 2-aminothiazole as a urea replacement, which led to the discovery of a series of novel *t*-butylphenoxy pyridinyl-2-aminothiazole analogs as potent P2Y₁ inhibitors.

MEDI 146

Discovery of small molecule P2Y₁ antagonists part III: C-N linked indolinyl diaryl ureas as novel antiplatelet agents

Jennifer X Qiao¹, *jennifer.qiao@bms.com*; Tammy C Wang¹; Réjean Ruel¹; Carl Thibeault¹; Sheldon Hiebert¹; Gilles Bouthillier¹; John Lloyd¹; Zulan Pi¹; Alexander Kover¹; Ji Hua²; Laura A Price²; Qimin Wu²; Joanna Zheng²; Ming Chang²; Christine Huang²; Jeffrey S Bostwick²; Anne B Stewart²; William A Schumacher²; Carol A Watson²; Pancras C Wong²; Robert Rehfuß²; Ruth R Wexler¹; Patrick Y.S. Lam¹. (1) Medicinal Chemistry, Bristol Myers Squibb, Pennington NJ 08534, United States (2) Bristol Myers Squibb, United States

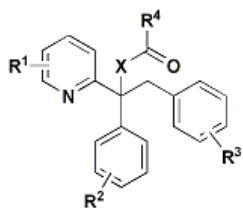
Two distinct G protein-coupled purinergic receptors, P2Y₁ and P2Y₁₂, mediate ADP driven platelet activation. The clinical effectiveness of P2Y₁₂ blockade is well established. Recent preclinical data suggests that P2Y₁ and P2Y₁₂ inhibition provide equivalent antithrombotic efficacy, while targeting P2Y₁ has the potential for reduced bleeding liability. BMS previously identified a series of *t*-butylphenoxy pyridinyl urea analogs as small molecule P2Y₁ antagonists. In this presentation, we will describe our SAR efforts focused at identifying *t*-butylphenoxy replacements, which led to the discovery of novel C-N linked indolinyldiaryl urea analogs as potent P2Y₁ antagonists. The dose-dependent effects of the lead compound in this series were demonstrated in rat models of thrombosis and hemostasis.

MEDI 147

Diphenylpyridylethanamines (DPPE) as novel cholesterol ester transfer protein (CETP) inhibitors

Lalgudi S Harikrishnan, *lalgudi.harikrishnan@bms.com*; Muthoni G Kamau; Heather J Finlay; Ji Jiang; James Li; Jennifer X Qiao; Tammy C Wang; Christopher B Cooper; Michael A Poss; Mark E Salvati; Ruth R Wexler; Leonard P Adam; David S Taylor; Alice Ye A Chen; Xiaohong Yin; Doree F Sitkoff; Carolyn A Weigelt; Ramakrishna Seethala; Tara L Peterson; Michael A Galella; Atsu Apedo; David S Nirschl; Katy VanKirk; Arthur V Miller; Christine S Huang; Ming Chang; Xue-qing Chen; R. Michael Lawrence. Bristol-Myers Squibb Company, Princeton NJ 08543, United States

Elevation of plasma high density lipoprotein cholesterol (HDL-C) is a promising approach for the potential treatment of atherosclerosis. Advanced clinical compounds that inhibit CETP increase HDL-C levels in humans. In this presentation, we disclose the discovery of a new ester series of CETP inhibitors, **1**, and the further optimization of the ester to provide the DiPhenylPyridylEthanamine series, **2** (DPPE). Additional optimization of the quaternary aryl/heteroaryl groups and series SAR will be presented leading to key compounds with *in vitro* and *in vivo* potency.



1 (X = O) Ester Chemotype
2 (X = NH) DPPE Chemotype

MEDI 148

Phenethylaminoheterocycles as Kv1.5 ion channel inhibitors

James A Johnson¹, james.a.johnson@bms.com; Ningning Xu¹; Yoon Jeon¹; Heather J Finlay¹; Alexander Kover¹; Mary L Conder²; Huabin Sun²; Danshi Li²; Paul Levesque²; Ling Li¹; Mei-Mann Hsueh³; Timothy W Harper³; Ruth R Wexler¹; John Lloyd¹. (1) Department of Discovery Chemistry, Bristol-Myers Squibb Research and Development, United States (2) Department of Biology, Bristol-Myers Squibb Research and Development, United States (3) Department of Preclinical Candidate Optimization, Bristol-Myers Squibb Research and Development, United States

Atrial fibrillation is a pervasive heart rhythm disorder distinguished by a shortened repolarization phase of the action potential of atrial myocytes and an abbreviated atrial effective refractory period (ERP). Kv1.5 ion channels conduct the ultrarapid delayed rectifier current (I_{Kur}) that contributes to this repolarization. Because Kv1.5 channels are functionally expressed in the atrium but not the ventricle, selective inhibition of I_{Kur} potentially leads to prolongation of the atrial ERP without ventricular effects. Phenethylaminoheterocycles have been prepared and assayed for inhibition of human recombinant Kv1.5 potassium ion channels as a potential approach to the treatment of atrial fibrillation. The synthesis and activity of the compounds, as a well as pharmacokinetic and pharmacodynamic properties, will be described.

MEDI 149

Alkaloid purification strategies for flash chromatography

Jack E. Silver, jsilver@teledyne.com; **Paul Bellinghausen**, pbellinghausen@teledyne.com; **Nancy Fowler**, nfowler@teledyne.com. Applications, Teledyne Isco, Lincoln NE 68504, United States

Alkaloids are common compounds derived from natural products. Many alkaloids are also synthesized for their medicinal properties. Alkaloids are challenging to purify on silica due to their polarity and basicity. The use of appropriate solvents and columns allow facile purification of this class of compounds. Examples are provided for silica, C18, ion exchange and alternative media such as diol and amine.

MEDI 150

Strategies for the flash purification of highly polar compounds

Jack E. Silver, *jsilver@teledyne.com*; **Paul Bellinghausen**, *pbellinghausen@teledyne.com*; **Nancy Fowler**, *nfowler@teledyne.com*. Applications, Teledyne Isco, Lincoln NE 68504, United States

Highly polar compounds, such as basic molecules and water soluble dyes, pose unique challenges for purification. They can bind to the media, or in the case of C18, elute without media interaction thereby preventing purification of the compound in both cases. Highly aqueous purifications on a new flash C18 media is demonstrated using dyes. HILIC is also explored to purify polar compounds on silica, diol, and amine columns.

MEDI 151

Novel series of piperaziny-pyridine ureas as antagonists of the purinergic P2Y₁₂ receptor

Peter Bach, *Peter.Bach@astrazeneca.com*. Department of Medicinal Chemistry, AstraZeneca R&D, Molndal 43183, Sweden

A novel series of P2Y₁₂ antagonists for development of drugs within the antiplatelet area is presented. The synthesis of the piperaziny-pyridine urea derivatives and their structure-activity relationships (SAR) are described. Several compounds showed P2Y₁₂ antagonistic activities in the sub-micromolar range.

MEDI 152

Green chemistry at AstraZeneca R&D Montreal: Focus on solvent selection

Mehrnaz Pourashraf¹, *mehrnaz.pourashraf@astrazeneca.com*; **François Samson-Thibault**¹; **Andrew Wells**²; **Michael Laplante**¹; **Louis-David Cantin**¹; **Christopher Walpole**¹; **Miroslaw J. Tomaszewski**¹; **Pascal Turcotte**³. (1) AstraZeneca R&D, Montreal Quebec H4S 1Z9, Canada (2) AstraZeneca Process R&D, Charnwood LE11 5RH, United Kingdom (3) Boehringer Ingelheim, Laval Quebec H7S 2G5, Canada

During the process of drug development, Volatile Organic Compounds (VOCs) are released to the atmosphere through the use of solvents in manufacturing processes and research and development activities. VOCs result mainly from the use of chlorinated and non-halogenated solvents in drug synthesis and contribute to the creation of smog, which is harmful to both human health and the environment. A few years ago, AstraZeneca undertook measures to eliminate or reduce the impact of toxic chemicals that are released during drug synthesis. To achieve this goal, our engineers and chemists began collaborations with scientists of other pharmaceuticals companies in order to find new and greener ways to work in chemistry. The application of these alternatives is not limited to drug manufacturing but is also encouraged in our research units. The measures taken at our site, AstraZeneca R&D Montreal, aim to reduce the

consumption of harmful solvents, particularly halogenated solvents, by replacing them with ones which are more environmentally friendly. In addition to this, some new green solvents have been introduced into the regular work of our chemists. Although the consumption of solvents and chemicals in discovery is typically lower than process and manufacturing sites, it is still important that green chemistry is used where possible in the early stage of research since it will be then applied to scale-up and development activities.

MEDI 153

Novel hydrogen sulfide releasing agents

Yu Zhao, dtzhaoyu@wsu.edu; Hua Wang; Ming Xian. Department of Chemistry, Washington State University, Pullman WA 99164, United States

Hydrogen sulfide (H₂S), an emerging signaling molecule, plays important roles in biological systems. However, the research on H₂S has been hindered by the lack of controllable H₂S releasing agents, i.e. H₂S donors, which could mimic the slow and continuous H₂S generation process *in vivo*. Since S-N bonds are unstable and easy to break under certain conditions, we envision that *N*-mercapto compounds are potential H₂S donors and structural modification could regulate rate/capability of H₂S release from these donors. We have synthesized and evaluated several types of *N*-mercapto based H₂S donors. In this presentation, our progress in this field will be discussed.

MEDI 154

QSAR approach in exploring diverse biological activities of *Aconitum* and *Delphinium* sp. alkaloids

Malakhath Turabekova^{1, 2}, malohathon@yahoo.com; Bakhtiyor Rasulev¹; Farkhad Dzhakhangirov³; Danuta Leszczynska²; Jerzy Leszczynski¹. (1) Interdisciplinary Center for Nanotoxicity, Department of Chemistry and Biochemistry, Jackson State University, Jackson MS 39217, United States (2) Department of Civil and Environmental Engineering, Jackson State University, Jackson MS 39217, United States (3) Department of Pharmacology and Toxicology, Institute of Chemistry of Plant Substances AS RUZ, Tashkent 100170, Uzbekistan

Uzbekistan based research unit (ICPS) has been engaged for many decades in isolation, purification, modification and pharmacological profile studies of diterpenoid alkaloids found in *Aconitum* and *Delphinium* plant sp. locally growing in Central Asia. These alkaloids have been the targets of considerable interest of medicinal chemists for a broad range of demonstrated pharmacological activities including arrhythmogenic (neurocardiotoxic), local anaesthetic, antiarrhythmic, curariform, analgesic, hypotensive, anti-inflammatory, spasmolytic, neurotropic and psychotropic. For the last few years our experimental research is actively accompanied by the computer aided drug design methods. Here we report results of our molecular modelling studies and extensive

QSAR analysis for toxicity, arrhythmogenic, antiarrhythmic, curare-like and local anaesthetic activities established earlier for diterpenoid alkaloids from our in-house collection. We showed that our results may serve as a good template for revealing some rules for enhancing potency and selectivity of studied alkaloids and more new promising medicinal candidates

MEDI 155

Synthesis of bicyclic peptidomimetics scaffolds

Stéphane De Cesco, *stephane.decesco@mail.mcgill.ca; Mitchell Huot; Nicolas Moitessier. Department of Chemistry, McGill university, Montréal Québec H3A2K6, Canada*

Peptides are often natural ligands for enzymes and/or receptors. Despite their great therapeutic potential the lack of metabolic stability has limited their use. Therefore designing new scaffolds that replace natural peptides had become of great interest. We present here our efforts toward the design and development of bicyclic scaffolds mimicking a large variety of dipeptides. Synthesis started from three commercially or readily available building blocks and final products are obtained in only two steps and one purification. The convergent and expedient aspect of the synthesis allowed us to quickly introduce diversity with no further synthetic efforts. Work toward the asymmetric version of the scaffold will also be presented.

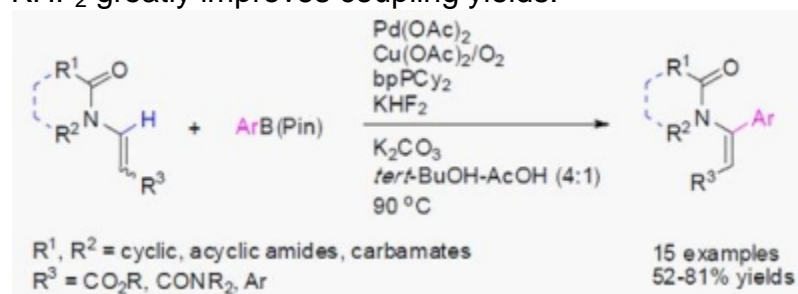
MEDI 156

Facile synthesis of highly substituted enamides via oxidative Heck reaction

Yu Liu, *liuy0055@ntu.edu.sg; Dan Li; Cheol-Min Park. Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore Singapore 637371, Singapore*

Enantiomerically pure beta-amino acids and their derivatives are important building blocks for the synthesis of beta-peptides, beta-lactam antibiotics, and many important drugs. Among these synthetic methods, straightforward asymmetric hydrogenation of beta-aminoacrylic acid derivatives represents one of the simplest routes. And functionalization of beta-amidoacrylates under Heck conditions has been limited to those with an unsubstituted vinyl group. We report herein oxidative Heck cross-coupling conditions that allow for the synthesis of highly substituted enamides. The study reveals that the use of pinacol boronates combined with 2-(dicyclohexylphosphino)biphenyl and

KHF₂ greatly improves coupling yields.

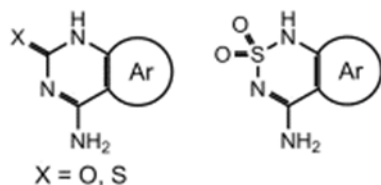


MEDI 157

Allosteric modulation of human sweet receptor as a novel approach to enhance sweet taste

Xiao-Qing Tang, xiao-qing.tang@senomyx.com; Catherine Tachdjian; Donald S Karanewsky; Xiaodong Li; Guy Servant; Feng Zhang; Qing Chen; Hong Zhang; Melissa S Wong; Vincent Darmohusodo; Goran Petrovic; Sara Adamski-Werner; Jeffrey Yamamoto; Joseph R Fotsing. Senomyx, Inc., San Diego CA 92121, United States

The steady increase of the daily consumption of dietary sugar over the last decades may have contributed to the obesity crisis and the early onset of type 2 diabetes observed in many developed countries. As a result, various noncaloric sweeteners have been developed to reduce dietary sugar intake; however, many are characterized by off-taste, delayed onset, or lingering of sweetness, and fail to mimic the real sugar taste. We present here a unique approach to develop positive allosteric modulators (PAMs) of the human sweet receptor to enhance the sweet taste of sugars without producing off-tastes. Sweet taste is mediated by an obligatory heterodimeric receptor composed of two subunits called T1R2 and T1R3. These two subunits correspond to class C GPCRs characterized by a Venus Fly Trap (VFT) domain at the N-terminus linked to the C-terminal heptahelical transmembrane domain (TMD) via a cysteine rich domain (CRD). We used a cell based assay for the human sweet taste receptor, high throughput screening, assay-guided lead optimization and taste testing with trained panelists to identify positive allosteric modulators (PAMs) that could allow a reduction of the amount of sweeteners used in consumer products. In taste tests these PAMs do not have intrinsic sweetness, but significantly increase the sweetness of a low amount of sucralose or sucrose.



MEDI 158

Empowered antibodies for cancer therapy

Peter D. Senter, *psenter@seagen.com. Seattle Genetics, Inc., Bothell WA 98121, United States*

A great deal of interest surrounds the use of monoclonal antibodies (mAbs) for cancer therapy. While significant activities have been found for such mAbs as trastuzumab, cetuximab, bevacizumab, and rituximab, there are many examples of mAbs that recognize tumor associated antigens but are devoid of significant activities in preclinical and clinical studies. One of the most powerful strategies for enhancing mAb activity involves the generation of antibody drug conjugates (ADCs) for selective delivery of anticancer drugs to tumor cells. This is an area that has advanced significantly, based on recent clinical studies with SGN-35 (brentuximab vedotin), an anti-CD30-auristatin antibody conjugate in patients with Hodgkin lymphoma and anaplastic large cell lymphoma. Brentuximab vedotin incorporates advancements and insights in drug and linker design, conjugation technology, and target antigen selection for mAb-mediated drug delivery. The presentation will overview the science and data behind this promising new agent.

MEDI 159

Protein medicinal chemistry with an expanded genetic code

Ho S. Cho, *ho.cho@ambrx.com. Department of Technology, Ambrx, Inc., La Jolla CA 92122, United States*

Traditional small molecule medicinal chemistry is empowered by a sizable repertoire of structural diversity that has been embellished by more than a century of advances in synthetic methodology. In analogy, protein chemistry is in its infancy where structural diversity has been largely limited to the optimization that can be performed with the set of chemical groups present in the natural 20 amino acids. The ability to incorporate novel amino acids using an expanded genetic code provides a unique and highly powerful tool for protein chemists. We have pioneered the application of this novel technology for medicinal chemistry purposes and advanced multiple drug candidates to human testing. The technological foundation of the work has expanded from the initial demonstration in *E. coli* and 4-helix bundle based proteins to numerous other proteins and expression systems. It is the intention of this lecture to provide a state-of-the-art demonstration of the technology through presentation of a few select projects.

MEDI 160

Targeted delivery of imaging and drug cargo using synthetically modified viral capsids

Matthew B. Francis, *mbfrancis@gmail.com. Department of Chemistry, University of California, Berkeley, Berkeley California, United States and Materials Sciences Division, Lawrence Berkeley National Laboratory, Berkeley California, United States*

Nanoscale materials offer promising new platforms for the tissue-specific delivery of therapeutic cargo. Through appropriate surface modification, multiple copies of a desired targeting group can be displayed to direct these carriers to cell surface markers of interest. The use of hollow structures allows drug molecules and radiolabels to be sequestered within the assemblies, protecting them from premature degradation and masking their influence on biodistribution. To realize this potential, we have developed a series of site-selective chemical reactions to convert the protein shell of a virus into a coordinated set of targeted delivery agents. Peptides, antibody fragments, and aptamers have been installed on the external surfaces, and the inside of each capsid has been modified to house high-relaxivity MRI contrast agents and F-18 labels for PET imaging. The new protein modification strategies that have enabled the construction of these carriers will serve as the focus of this presentation.

MEDI 161

Spying on protein conformation, function and assembly using fluorogenic small molecules

Alanna Schepartz, *alanna.schepartz@yale.edu. Department of Chemistry, Yale University, New Haven CT 06520, United States*

Exploration across the fields of biology, chemical biology, and medicine has led to an increasingly complex, albeit incomplete view of the interactions that drive life's processes. The ability to monitor and track the movement, activity, and interactions of biomolecules, especially in living cells, is an essential part of this investigation. As chemists, we seek to understand these macromolecular events at a level of resolution that reveals their energetic and structural underpinnings. This objective demands the development of increasingly sophisticated methods to image not just the location of a biomolecule of interest, but also to reveal its structure and function. Our approach to this goal exploits a family of fluorogenic small molecules whose fluorescence is dependent on an interaction with a discrete protein sequence, conformation or assembly. This lecture will describe recent progress in this area, with an emphasis on the fundamental concepts that underlie the use of these molecules for experiments in living cells.

MEDI 162

Realizing the potential of antibody-drug conjugates in cancer: Selection of the right cytotoxic agent and linker

Ravi V. J. Chari, *ravi.chari@immunogen.com. ImmunoGen, Inc., Waltham MA 02451, United States*

We have exploited the tumor specificity of monoclonal antibodies for the targeted delivery of highly cytotoxic drugs that are otherwise too toxic to be used on their own. Our highly potent tubulin interacting maytansinoid compounds DM1 and DM4, have been incorporated in Antibody-Maytansinoid Conjugates (AMCs). The design of each maytansinoid conjugate has been tailored to achieve optimal activity for the specific cancer target. Linkers have been designed such that the AMCs are stable in circulation, and are virtually non-toxic until they bind to the tumor cell through the antibody component. They are then activated specifically by the tumor into potent cytotoxic agents. Multiple AMCs are currently in clinical evaluation. The design and development from the bench to the clinic of these conjugates will be discussed. Mechanistic studies on the activation of AMCs, and recent advances in linker design and new cytotoxic agents for use in antibody-drug conjugates will be highlighted.

MEDI 163

Trastuzumab emtansine (T-DM1) for the treatment of HER2-positive breast cancer

Mark X. Sliwkowski, *marks@gene.com. Research Oncology, Genentech, Inc., South San Francisco CA 94070, United States*

Trastuzumab-DM1 (T-DM1; trastuzumab emtansine) is composed of the humanized antibody trastuzumab and DM1, a maytansinoid derivative, linked with a nonreducible thioether linker, N-succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC, designated MCC after conjugation). Maytansinoids are natural products that are potent antimitotic agents, which like the *vinca alkaloids* prevent microtubule assembly. Due in part to their impressive potency, maytansinoids were investigated as drugs for conjugation to monoclonal antibodies. Derivatives of maytansinoids were synthesized to allow chemical conjugation to proteins using disulfide linkers. The realization that the endocytic pathway is not reducing and our empirical experimental observations led us to conclude that the more stable thioether linkage was better suited for maytansinoid coupling to trastuzumab. Early promising clinical data were recently generated in patients whose tumors have progressed on HER2-directed therapies.

MEDI 164

WITHDRAWN

MEDI 165

New and innovative business models that foster external collaborations while balancing risk and reward

Richard D Connell, *richard.connell@pfizer.com. External Research Solutions COE, Pfizer Inc, Groton CT 06340, United States*

Big Pharma has a need and desire to externalize some aspects of research in order to gain access to key thought leaders or to new technologies or capabilities that do not exist in house. To promote these collaborations, many companies have Business Development groups who scan the R&D environment looking for partnerships in the biotech or academic communities. Other reasons to build external networks of partners include a desire to variabilize costs associated with services or assets that exist in the marketplace. Such external relationships provide flexible capacity to Pharma and enable a more staffing model that can rise or fall as the business needs dictate. These well defined, transactional, or service-derived relationships tend to fall into the domain of Contract Research Organizations (CROs) and tend to be managed by outsourcing and procurement professionals. As the push for increased productivity continues, and Research budgets continue to feel the strain of finite resources, there is increased pressure to look at the new partnership models that help Pharma deliver its portfolio of promising medicines in a cost effective way. In this talk, examples of new partnership models that externalize Research assets and/or tap into the “wisdom of the crowds” will be discussed. These examples described in this talk share the common theme of increasing the efficiency of the Research engine.

MEDI 166

Translational therapeutics development at NIH

Christopher Austin, *austinc@mail.nih.gov*. NIH Center for Translational Therapeutics, National Institutes of Health, Bethesda Maryland 20892, United States

The explosion in mechanistic understanding of human physiology in health and disease, exemplified by the Human Genome Project and its successors, has provided a deluge of potential new targets for therapeutic development. At the same time, evolution of technologies and operational systems for drug discovery has allowed investigators and institutions in the public sector to contribute directly to new therapeutics discovery in a more vigorous way, particularly for rare and neglected diseases. Over the last decade, the NIH has built a variety of programs which complement drug discovery efforts in the biopharmaceutical sector, principally in two areas: (a) science, technology, tool, and paradigm development to improve scientific understanding and efficiency of the therapeutics discovery process, and (b) early stage drug development programs to de-risk projects particularly for rare and neglected diseases, making them more amenable to biopharmaceutical adoption despite their low expected ROI. The mission and accomplishments of these programs will be discussed.

MEDI 167

Evolving computational tools to cope with ever increasing data volume - focused innovation

Chris Culberson, *chris_culberson@merck.com*. Merck & Company, Inc., United States

Scientific enhancements and innovations have allowed us to effectively synthesize molecules and measure their physical and biological properties with ever increasing speed. However, with the increase, a weakness in our ability to keep pace with the analysis of those data has been highlighted. Computational chemists are responsible for the initial phases of the data analysis, as well as distilling the analysis into lessons learned to lessen the impact of the increased data volume. We can take advantage of innovations in general data analysis techniques and remove the current bottleneck only to expose the next set of tools not up to the task. In this talk, we will discuss the current tools, perceived bottlenecks and future directions for focused innovation in the computational chemistry toolbox.

MEDI 168

Future role of Medicinal Chemistry and its maturation to Chemical Biology

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Medicinal Chemistry is often referred to as a “mature science” evoking images of the grandfather of drug discovery – geriatric, slow and even grumpy. This talk will outline a chain of thoughts which conclude that chemistry has a wider role to play in innovative drug discovery than it is currently permitted by industry to have. In that respect, three Chemical Biology approaches will be briefly discussed: i) small molecules that enable intracellular delivery of macromolecules into cytosol, ii) RNA as drug target for the regulation of gene expression, and iii) regenerative medicine through small molecules that differentiate pluripotent stem cells. If successful, the application of Chemical Biology within industry holds the promise of delivering innovation in healthcare that reaches far beyond the current limitations of traditional Medicinal Chemistry.

MEDI 169

Academic labs and the discovery of innovative new medicines: From disease biology to experimental compounds with drug-like properties

B Michael Silber, *msilber@ind.ucsf.edu. Department of Neurology and Bioengineering and Therapeutic Sciences, University of California San Francisco Institute for Neurodegenerative Diseases, San Francisco California 94143, United States*

Academic labs have been responsible for virtually all of the basic science discoveries that have translated into innovative new medicines, typically discovered and developed by pharmaceutical or biotechnology companies. There is widespread acceptance that large pharmaceutical and biotechnology companies are no longer able to generate enough innovative experimental compounds to support Phase I – III development pipelines from internal research. What is needed are new clinically validated targets, new compounds with good drug-like properties, along with suitable biomarkers in target patient populations, especially in areas with high unmet medical need. Academic labs

have the potential to contribute, from disease biology and therapeutic hypothesis, to the discovery and early development of experimental compounds with good drug-like properties, directly and through collaborations with pharmaceutical and biotechnology companies. Collaboration is in the best interests of patients and society if it accelerates the translation of basic science to new medicines that address unmet medical needs.

MEDI 170

How to beat back the commoditization of the pharmaceutical industry?

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The long-predicted pharmaceutical innovation crisis has arrived. New drug approvals for big pharma can no longer replace sales lost to generics; \$130 billion of US sales face patent expiration; R&D spending is under the knife; and the patent cliffs ahead could make things worse. Yet, as the industry faces commoditization, the ingredients of success are at hand: we have talent, capital, and an accumulating number of cutting-edge discoveries waiting to be translated into useful therapies. How to combine these ingredients into a winning recipe? This session will explore the key questions that define a successful drug R&D organization: what is the focus? how to manage it? how to fund it? how to mitigate risk effectively? It will draw upon what research has shown to produce innovation, and will offer actionable ideas to rebut the dire predictions about the industry.

MEDI 171

Chemical basis of pharmacology

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So dominant has molecular pharmacology become that it is difficult to remember that 25 years ago it was only an aspiration. Today we understand drug activity through the specific receptor molecules with which they interact. To discover new leads we screen libraries against such targets, and these targets are related by sequence identity. A generation ago this view was inverted: investigators began with small molecules and sought targets, and receptors were related by the ligands that bound them. Here we return to this classic idea, seeking unexpected similarities. We compare sets of ligands for over 3000 targets to one another. The relationships that emerge predict previously unknown off-targets for drugs and reagents, 30 of which have been tested, largely with Bryan Roth (UNC-CH), with potencies ranging from 1.2 nM to 14 μ M. Applications to adverse drug reactions, mechanism of action, new target opportunities, and phenotypic screens will be considered.

MEDI 172

Multiplex proteomic measurements in drug and diagnostic research and development

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Plasma proteins and secreted proteins, released from cells and surrounding tissues, contain important biological information with the potential to inform early diagnostic, prognostic, and therapeutic decisions in research and medicine. SomaLogic has developed a proteomic biomarker discovery and diagnostic application technology that measures 1033 human proteins in low sample volumes (~8 uL of serum/plasma, tissue homogenate) with a high-performance, high-throughput, and cost effective assay. The assay achieves low limits of detection (1 pM average), ~7 logs of overall dynamic range, and ~5% average coefficient of variation. This technology is enabled by a new class of DNA aptamers – “SOMAmers” – that contain novel chemically-modified nucleotides, which greatly expand the physicochemical diversity of the large combinatorial SELEX libraries from which they are selected. Proteins are measured with a process that transforms a signature of protein concentrations into a representative DNA concentration signature, which is quantified with a DNA microarray, bead-based hybridization, or qPCR. We have demonstrated the utility of this technology in a large clinical biomarker discovery studies as well as therapeutic R & D applications.

MEDI 173

Discovery of CNS drug candidates for treatment of Parkinson's disease and Alzheimer's disease

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Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by loss of dopamine-producing cells in the substantia nigra, which results in a syndrome of movement disorders. Adenosine A_{2A} antagonists have potential as a non-dopaminergic treatment to control the motor symptoms of PD. The discovery of the potent adenosine A_{2A} antagonist Preladenant, which has shown efficacy in several preclinical models, and improved symptoms of PD when dosed in combination with L-DOPA, will be described. Alzheimer's disease (AD) is a progressive, ultimately fatal neurodegenerative disease with an average life expectancy of 7-10 years after diagnosis. A pathological hallmark observed in the brains of AD patients is extracellular amyloid plaques, mainly composed of an amyloid β peptide 42 amino acids in length (A β 42). Beta amyloid is produced from the amyloid precursor protein (APP) by the action of the enzymes BACE-1 and gamma secretase. Blocking the action of BACE-1 with small molecule inhibitors is a promising disease modifying therapy that could halt or even reverse the progression of AD. Using a fragment screening approach, coupled

with X-ray crystallography, we have discovered potent BACE inhibitors with promising in vivo efficacy. These inhibitors, and their activity in preclinical AD models will be described.

MEDI 174

Substrate activity screening: A fragment-based method for inhibitor discovery

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Substrate activity screening (SAS) is a fragment-based method for the rapid development of novel, drug-like enzyme inhibitors. The method consists of three steps: (1) a diverse library of low molecular weight substrates is screened against an enzyme target to identify lead fragments, (2) the identified fragments are rapidly optimized by subsequent rounds of analogue synthesis and evaluation, and (3) the optimized substrates are converted to inhibitors by direct incorporation of mechanism-based inhibitor pharmacophores. Because the assay requires productive substrate binding and turnover, false positives often seen in traditional high-throughput inhibitor screens are eliminated. Additionally, catalytic substrate turnover results in signal amplification enabling the identification of very weakly active lead fragments. The successful application of the SAS approach to the rapid identification of novel, potent and selective small molecule inhibitors to therapeutically relevant proteases and phosphatases will be presented.

MEDI 175

Award Address (E.B. Hershberg Award for Important Discoveries in Medicinally Active Substances sponsored by Schering-Plough Research Institute). CPP-115: A GABA aminotransferase inactivator and new treatment for epilepsy and drug addiction

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An imbalance in the levels of the inhibitory neurotransmitter g-aminobutyric acid (GABA) and the excitatory neurotransmitter glutamate can lead to convulsions. Inhibition of g-aminobutyric acid aminotransferase (GABA-AT), the enzyme responsible for the degradation of GABA, increases the GABA levels, which has been shown to produce an anticonvulsant effect; it also has been found to lead to a new treatment for drug addiction. We have synthesized a variety of mechanism-based inactivators of this enzyme and studied their mechanism of action. In this lecture I will discuss the design and mechanism of our GABA-AT inactivators and how these compounds led to the discovery of CPP-115, a molecule that is currently in preclinical development for the treatment of epilepsy and drug addiction. In vitro mechanistic studies and in vitro and in vivo efficacy, ADME, and toxicology studies of CPP-115 will be presented.

MEDI 176

Thermodynamics-based drug design: Achieving high selectivity

Ernesto Freire, *ef@jhu.edu. Biophysics, Johns Hopkins University, Baltimore Maryland 21218, United States*

High affinity and selectivity are two essential properties of drug molecules. Selectivity has been difficult to achieve, especially for targets that belong to large families of structurally and functionally related proteins. There are essentially two ways of improving selectivity during lead optimization: 1) a chemical modification of the lead compound improves the affinity towards the target to a higher extent than to off target molecules; and, 2) a chemical modification of the lead compound actually lowers its affinity towards off target molecules. Maximal selectivity is achieved when both situations apply simultaneously. Analysis of several protease inhibitors that vary by a single functionality indicates that non-polar functionalities can follow either mechanism while polar functionalities follow the second one. The actual mechanism reflects the balance of desolvation and target interactions and is revealed in the changes in thermodynamic signature associated with the compound modification, which can be determined by Isothermal Titration Calorimetry (ITC). ITC can be used as an important tool for selectivity optimization.

MEDI 177

Fragment-based drug discovery: A medicinal chemists perspective

Andrew Woodhead, *a.woodhead@astex-therapeutics.com. Department of Medicinal Chemistry, Astex Therapeutics, Cambridge Cambridgeshire CB1 0QA, United Kingdom*

Five years ago most scientists did not consider low molecular weight fragments (MW = 120-250) with only mM to uM binding affinities to be attractive starting points for drug discovery programs. However, today there is widespread acceptance that these fragments can be progressed into nM lead series and on into clinical trials. Reported examples include clinical candidates that target different protein families such as kinases (CDK, Aurora, Akt, raf), protein-protein interactions (Bcl-X_L), ATPases (HSP-90) and proteases (MMP 2&9). This presentation has two parts. Firstly, a general overview of the techniques associated with fragment based drug discovery. The second part of the talk will cover specific examples of fragment optimisation from Astex, highlighting the integration of structural information into medicinal chemistry and the influence this has on compound design. Murray CW, Rees DC: **The rise of fragment-based drug discovery**. *Nat. Chem.* 2009, **1**:187-192.

MEDI 178

Nature of the hydrogen bond and its role in medicinal chemistry

Daniel Cheney, *daniell.cheney@bms.com. Bristol-Myers Squibb, United States*

Hydrogen bonding plays an essential role in biomolecular assembly and recognition, and is a key determinant in drug potency, selectivity and pharmacokinetic and related properties. An overview will be given of hydrogen bonding in the context of medicinal chemistry. Topics will include physical and structural aspects of the hydrogen bond, the estimation and comparison of hydrogen bonding strengths of common drug like moieties, the role of hydrogen bonding in protein – drug complexation, and considerations of hydrogen bonding in the adjustment of physical properties which impact on pharmacokinetics.

MEDI 179

From fine tuning to major overhaul: Applications of deuterium medicinal chemistry

Scott L Harbeson, *sharbeson@concertpharma.com. Concert Pharmaceuticals, Inc., Lexington MA 02421, United States*

Computational and synthetic tools have enabled a more rational approach to lead optimization when addressing ADMET challenges in a molecule or scaffold. However, the structural changes that are brought to bear on a molecule (solubilizing groups, eliminating or blocking metabolic sites, isosteric replacements, prodrugs, etc.) can alter the activity and specificity profiles of the compound, thereby necessitating assessment of both the ADMET and pharmacology during optimization. In certain cases, balancing these often competing molecular requirements results in agents with non-optimal metabolic properties. Deuterium medicinal chemistry provides an optimization tool that can effect both subtle and marked changes in ADMET properties with minimal perturbation of the intrinsic pharmacology of a compound. This presentation will focus on specific examples where deuterium has enabled improvements in therapeutic entities through decreased clearance (longer half-life), increased bioavailability, or metabolic switching away from undesired metabolites. In select cases, deuterium medicinal chemistry can yield improvements in safety, efficacy, and/or tolerability without significantly altering the biochemical potency and selectivity of a compound.

MEDI 180

Polar C-F bond and its potential for influencing molecular design in bioorganic and medicinal chemistry

David O'Hagan, *do1@st-andrews.ac.uk. University of St. Andrews, United Kingdom*

The C-F bond is the most polar in organic chemistry and this imparts extreme properties which can be used to influence the conformation of organic molecules through consequent stereoelectronic and electrostatic effects. We are interested in preparing molecules that explore the stereoelectronic influence of fluorine such that predictions

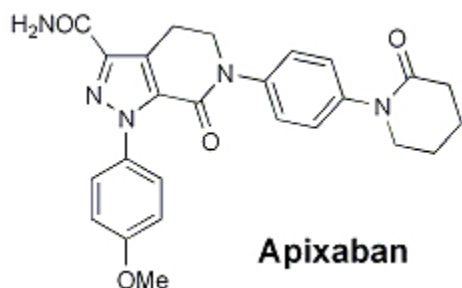
relating to molecular conformation can be made. These aspects will be outlined in a number of case studies. The conformations of alkane stereoisomers carrying upto six fluorine atoms arranged along a hydrocarbon chain will be described. Also the influence of the C-F bond in heterocyclic and alicyclic ring conformations will be explored and stereoselective fluorination of receptor agonists including eg. 3F-GABA and 3F-NMDA will be highlighted.

MEDI 181

Next generation oral anticoagulant: The discovery of Apixaban, a potent, selective, and orally bioavailable factor Xa inhibitor

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Thrombosis is the leading cause of death in developed countries and there is significant need for novel antithrombotics with an improved safety profile. Factor Xa is at the junction of the intrinsic and extrinsic pathways of the coagulation cascade. Preclinical data has demonstrated that blocking FXa is an effective approach for anticoagulation with improved safety profile. Utilizing structure-based drug design tools, we at Bristol-Myers Squibb have discovered a novel class of potent, selective and orally bioavailable Factor Xa inhibitors culminating in Apixaban. Apixaban is being evaluated in a series of ongoing or completed Phase III clinical trials.



MEDI 182

Dose selection for a direct and selective factor IXa inhibitor and its complementary control agent: Translating pharmacokinetic and pharmacodynamic properties of the REG1 System to clinical trial design

Christopher P Rusconi¹, *crusconi@regadobio.com*; Thomas J Povsic²; Mark Y Chan²; William A Wargin³; Robert A Harrington²; John H Alexander²; Richard C Becker²; Steven L Zelenkofske⁴; Mauricio G Cohen⁵. (1) Regado Biosciences, Inc, Durham NC 27701, United States (2) Division of Cardiology, Duke Clinical Research Institute, Durham NC, United States (3) ClinPharm Consulting, RTP NC, United States (4) Regado Biosciences, Inc, Basking Ridge NJ, United States (5) Cardiovascular Division, University of Miami Miller School of Medicine, Miami FL, United States

The REG1 Anticoagulant System consists of pegnivacogin (aka RB006), a direct coagulation FIXa inhibitor and anivamersen (aka RB007), its active control agent. Pegnivacogin is a single-stranded nucleic acid aptamer conjugated to a large molecular weight polyethylene glycol carrier. Anivamersen is a short oligonucleotide complementary to a portion of pegnivacogin. Binding of anivamersen to pegnivacogin irreversibly alters its structure, rendering pegnivacogin unable to interact with FIXa and thereby neutralizing its anticoagulant activity. Pegnivacogin is the first FIXa inhibitor to be evaluated in an arterial thrombotic indication, with RADAR, a phase 2b study of REG1 in ACS-PCI, being recently completed. The focus of this presentation will be the selection of doses of pegnivacogin for phase 2 studies, and the effectiveness of pegnivacogin in providing protection from ischemic events in ACS-PCI patients. The strategy used for selection of dose ranges of anivamersen for phase 2 studies will also be discussed as will the impact of REG1 on major bleeding in ACS-PCI.

MEDI 183

Discovery and development of the selective PAR-1 antagonist Atopaxar

Richard Clark¹, *r-clark@hhc.eisai.co.jp*; **Tetsuya Kawahara**¹; **Motoji Kogushi**¹; **Shinki Kawaguchi**¹; **Makoto Kotake**¹; **Fumiyoshi Matsuura**¹; **Takashi Musha**²; **Toshiyuki Matsuoka**²; **Nobuaki Sato**¹; **Syuichi Suzuki**¹; **Masahiro Takada**¹; **Taro Terauchi**¹. (1) *Tsukuba Research Labs., Eisai Co. Ltd, Tsukuba Ibaraki 300-2635, Japan* (2) *Department of Drug Fostering and Evolution, Eisai Co. Ltd, Tokyo 112-8088, Japan*

Thrombin stimulates human platelets, which are known to play a major role in arterial thrombotic diseases, through the activation of protease-activated receptor-1 (PAR-1) and protease-activated receptor-4 (PAR-4). It is thought that inhibiting the action of thrombin on PAR-1, its principal effector on human platelets, may provide a new therapeutic option for atherothrombotic disease with lower risk of bleeding complications. We obtained a non-peptide, small molecule PAR-1 antagonist (ER-97719-15) from high throughput screening using a receptor binding assay system. Subsequent modification of this compound led to Atopaxar (E5555) which is currently under clinical investigation. This presentation will describe how the original lead was developed into the clinical candidate, detail the pharmacological effects of E5555, and also present some clinical results with Atopaxar in patients with Acute Coronary Syndrome or high risk Coronary Artery Disease.

MEDI 184

Prasugrel, a third generation thienopyridine: Lab to patient

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The thienopyridine oral antiplatelet agents, ticlopidine and clopidogrel, are prodrugs that require metabolism in vivo to active metabolites that irreversibly inhibit the platelet

P2Y₁₂ ADP receptor. Clopidogrel's platelet inhibitory effects exhibit a relatively slow onset and are highly variable. In contrast, prasugrel, a more recent addition to the thienopyridine class, has a relatively faster onset of action and is associated with less antiplatelet variability. Because the active metabolites of these two agents are comparably potent, the faster and greater antiplatelet effects of prasugrel are explained by the more efficient conversion to its active metabolite. Results from the TRITON-TIMI 38 trial which compared prasugrel to clopidogrel in high risk ACS patients scheduled for PCI will be discussed.

MEDI 185

Development of dabigatran etexilate: A direct, reversible, oral thrombin inhibitor

Susan Wood¹, *susan.wood@boehringer-ingelheim.com*; Joanne van Ryn². (1) Department of Medical Affairs, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield CT 06877, United States (2) Department of CardioMetabolic Disease Research, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield CT 06877, United States

Dabigatran is a selective, reversible and potent inhibitor of thrombin and is orally available as the double prodrug, dabigatran etexilate. Antithrombotic efficacy of the compound has been demonstrated in a number of animal models of venous and arterial thrombosis. In addition, dabigatran inhibits thrombin-induced platelet aggregation. It has also been demonstrated in animal models of atherosclerosis and fibrosis to have protective effects on proliferation and promote plaque stability. Peak plasma concentrations of dabigatran in humans are achieved 1-2 hours after ingestion and the half-life in elderly volunteers is 12-14 hours. Dabigatran has a low potential for drug-drug interactions, does not interact with food and is predominantly renally excreted. For the first time it has been demonstrated clinically in patients with atrial fibrillation, that there may be an effective and safe alternative to warfarin for stroke prevention.

MEDI 186

Discovery of vorapaxar: A thrombin receptor antagonist with promising antiplatelet effects

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Vorapaxar is a thrombin receptor (also known as protease activated receptor-1 or PAR-1) antagonist that is being developed for the treatment of acute coronary syndrome (ACS) which comprises a spectrum of clinical conditions ranging from unstable angina to acute myocardial infarction. The initial PAR-1 lead was a synthetic analog of the natural product himbacine. Extensive lead optimization efforts led to the discovery of vorapaxar which is a competitive antagonist of PAR-1 with a K_i of 8.1 nM. In a preclinical cynomolgus monkey ex vivo platelet aggregation model vorapaxar inhibited agonist

induced platelet aggregation for > 24 h after oral administration at 0.1 mg/kg. In P-II clinical studies vorapaxar met the primary end point of lack of increased bleeding compared to placebo and also showed a numerical reduction in periprocedural myocardial infarction and major adverse cardiac events. Results from two major P-III clinical studies for ACS and secondary prevention of ischemic events are anticipated in the future.

MEDI 187

Discovery of the novel HCV NS3 protease inhibitor, GS-9451

Hyungjung Pyun, *ppyun@gilead.com*; Christopher Sheng; Todd Appleby; Ona Barauskas; Thomas Butler; Ruby Cai; Xiaowu Chen; Aesop Cho; Michael Clarke; Amy Corsa; Edward Doerffler; Magdeleine Hung; Mingzhe Ji; John Link; Xiaohong Liu; Rowchanak Pakdaman; Margaret Robinson; Brian Schultz; Chin Tay; Qiaoyin Wu; Jie Xu; Chris Yang; Huiling Yang; William Delaney; Choung Kim. Gilead Sciences, Foster City CA 94404, United States

GS-9451 has been identified as a specific HCV NS3 protease inhibitor and is currently in phase 2 clinical development for the treatment of chronic genotype 1 (GT1) HCV infection. It has an *in vitro* EC₅₀ ranging from 7-10 nM in both HCV 1a and 1b replicon assays and is highly selective (> 20000-fold) over all tested mammalian proteases. It exhibited [good aqueous solubility and excellent pharmacokinetic properties in animal model studies. We will discuss the SAR and pharmacokinetic optimizations that lead to the discovery of GS-9451.](mailto:Gilead%20Sciences,%20Inc.)

MEDI 188

Discovery of BMS-911543, a highly selective JAK2 inhibitor as clinical candidate for the treatment of myeloproliferative disease

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Myeloproliferative diseases (MPD) are clonal malignancies that arise from hematopoietic progenitors and characterized by overproduction of mature and functional blood cells. MPDs are classified into classic variants including polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). Significant medical need exists, as the current standard of care is only palliative and does not change the

course of these diseases. Recent discovery of activating mutations in the tyrosine kinase gene, JAK2, and constitutive activation of the JAK2-STAT pathway, in large number of the MPD patients has ignited considerable interest in these diseases and has highlighted JAK2 as a therapeutic intervention point for drug discovery efforts. However, high sequence homology with other JAK family members has posed a major challenge to the design of a selective JAK2 inhibitor. Given that other JAK family members are involved in regulation of immune function, it is important to maintain selectivity for JAK2 over family members in order to mitigate the risks associated with undesired immunosuppression. Several JAK2 inhibitors with varying selectivity profiles are currently being evaluated in preclinical setting as well as in the clinical trials. This presentation will focus on the discovery of a selective JAK2 inhibitor, BMS-911543, for the treatment of MPD. The talk will outline structure based drug design efforts towards achieving the desirable selectivity. The presentation will also discuss complete biological characterization of the lead candidates that eventually led to the selection of the clinical candidate, BMS-911543.

MEDI 189

Brain penetrant PI3 kinase inhibitors

Timothy P Heffron, *theffron@gene.com. Department of Discovery Chemistry, Genentech, South San Francisco CA 94080, United States*

The well documented deregulation of the PI3K/AKT/mTOR pathway in numerous tumor types has established a significant desire for PI3K inhibitors. Aberrant signaling through this pathway is observed in a significant majority of glioblastoma. Using *in silico* evaluations to prioritize compounds for synthesis, our program successfully identified several potent inhibitors of PI3 kinase capable of crossing the blood-brain barrier. This presentation will discuss the use of *in silico* tools to minimize efflux and brain tissue binding while simultaneously improving metabolic stability. *In vivo* tumor growth inhibition in relevant glioblastoma models will also be presented.

MEDI 190

Optimization of 5-aryl-3-benzyloxy-pyridin-2-ylamine series to minimize CYP3A4 inhibition potential: Discovery of Crizotinib (PF-02341066) for oncology applications

J. Jean Cui, *jean.cui@pfizer.com; Mitchell Nambu; Pei-Pei Kung; Michelle Tran-Dube; Hong Shen; Mason Pairish; Jia Lei; Jerry Meng; Funk Lee; Michele McTigue; Shinji Yamazaki; Gordon Alton; Helen Zou; James Christensen; Barbara Mroczkowski. La Jolla Laboratory, Pfizer PharmaTherapeutics Worldwide Research, San Diego CA 92121, United States*

3-Benzyloxy-5-phenyl-pyridin-2-ylamine was created as a class of potent and highly selective c-Met inhibitors based on the co-crystal structure of PHA-665752 with c-Met

kinase domain. However, 3-benzyloxy-5-phenyl-pyridin-2-ylamines showed strong inhibition of CYP3A4. Lead optimization of 5-aryl group for solving CYP inhibition issue and improving overall pharmaceutical properties was carried out. 3-Benzyloxy-5-pyrazol-4-yl-pyridin-2-ylamines demonstrated higher ligand efficiency (LE) and lipophilic ligand efficiency (LipE) with improved pharmaceutical properties, especially reduced CYP inhibition potential. Further optimization of *N*-substituents on 5-pyrazol-4-yl group generated clinic candidate PF-02341066 (Crizotinib), which demonstrated potent *in vitro* and *in vivo* c-Met/ALK inhibition, effective tumor growth inhibition in c-Met and ALK driven tumor models, and good pharmaceutical properties. Crizotinib is currently in Phase III clinical study, and demonstrates remarkable efficacies for Lung cancer patients with EML4-ALK fusion gene.

MEDI 191

Discovery and preclinical characterization of BMN 673, a highly potent and orally active PARP inhibitor as an anticancer agent

Bing Wang, *BWang@bmrn.com*; Daniel Chu; Yuqiao (Jerry) Shen; Ying Feng; Peter Myers; Leonard Post. BioMarin Pharmaceutical Inc., United States

The nuclear enzyme poly (ADP-ribose) polymerase has emerged as an important novel target in cancer therapy. It is activated by DNA damage and plays a critical role in single strand DNA breaks repair via base excision repair (BER) pathway. PARP inhibitors were initially developed as possible chemo-sensitization agents by preventing cancer cells from repairing DNA damage caused by cytotoxic drugs. The recent preclinical and early clinical results have shown that potent PARP inhibitors can also act as single agents to selectively kill cancer cells harboring defects in other DNA repairing proteins, such as the breast and ovarian cancer cells with BRCA-1 or BRCA-2 mutations. It is hypothesized that in the cancer cells with the mutations of BRCA-1 or BRCA-2, the double-strand DNA breaks caused by the accumulation of single-strand DNA breaks due to PARP inhibition could not be repaired and consequently would lead to cell death. In this presentation, we will disclose the discovery and characterization of BMN 673 (formerly LT-00673), the most potent PARP inhibitor reported to-date. In cultured human cancer cells, BMN 673 significantly enhances the cytotoxic efficacy of both temozolomide and SN-38 (active metabolite of Irinotecan). BMN 673 also demonstrates single-agent cytotoxicity in BRCA-1 and BRCA-2 mutant tumor cells. In animal PK studies, BMN 673 displays good oral bioavailability and pharmacokinetic properties that enable single daily dosing. Specifically, the presentation will focus on the identification of hit, SAR, and hit-to-lead-to-candidate optimization processes. The PK/PD characterization, which aided the selection of the candidate into the clinical development, will also be discussed. Currently, the Phase 1 clinical study of BMN 673 is underway.

MEDI 192

Reviving the dead: Re-evaluation and optimization of a former terminated lead series allows for the identification of a candidate CCR2 antagonist

Clark A Sehon¹, *clark.a.sehon@gsk.com*; Gren Wang¹; Andrew Viet¹; Terry Hughes²; Krista Goodman³; Brian Budzik⁴; Jing Zhang⁴; Pamela Haile¹; Tom Daniel⁴; Nathan Miller¹; Tamara Miskowski⁴; Dimitri Gotchev⁴; Minghua Gu⁵; Ryan Fox³; Hilary Eidam³; Ronggang Liu⁴; Michael Bury¹; Feng Ren⁴; Zhimin Du⁴; Deyou Sha⁴; Sarah Dowdell³; Xuan Hong²; Subhas Chakravorty²; Christine Webb⁶; Carla Cornejo⁶; Alan Olzinski⁷; Roberta Bernard⁷; Chris Evans²; Amanda Emmons²; Peter Gough⁸. (1) Department of Medicinal Chemistry, Immuno-Inflammation, GlaxoSmithKline, Collegeville PA 19426, United States (2) Platform Technology and Science, GlaxoSmithKline, United States (3) Department of Medicinal Chemistry, Metabolic Pathways, GlaxoSmithKline, United States (4) Department of Medicinal Chemistry, GlaxoSmithKline, United States (5) Department of Medicinal Chemistry, Infectious Diseases, GlaxoSmithKline, United States (6) Department of Biology, GlaxoSmithKline, United States (7) Department of Biology, Metabolic Pathways, GlaxoSmithKline, United States (8) Department of Biology, Immuno-Inflammation, GlaxoSmithKline, United States

The recruitment of monocytes/macrophages is a key process in the growth of atherosclerotic lesions and in the subsequent rupture of these plaques. CCR2 plays a key role in this recruitment and inhibiting this receptor should decrease the likelihood of atherosclerosis. Our initial sulfonamide lead series was highly selective and potent in the primary assay but was significantly less active in plasma, which significantly diminished in vivo efficacy. In parallel, after reviewing the historical data from previous efforts, the team decided to reevaluate a dipiperidine series. These dipiperidines were initially terminated due to poor 7-TM selectivity and the belief that an activity plateau had been reached. However, in comparison to the sulfonamide series, the dipiperidines did show promising activity in the presence of plasma and were significantly more potent in vivo. Therefore, the team elected to diversify and pursue the dipiperidines and through a combination of both rational design and array synthesis in which breakthroughs were made that improved both selectivity and potency. Recently, a compound was identified from the dipiperidine series with dramatically improved activity in the primary and human whole blood shape change assays and excellent 7-TM selectivity. This compound has excellent rat PK and p450 profiles and was recently selected as the first CCR2 candidate. The strategy employed in the identification of this compound and pertinent SAR will be discussed.

MEDI 193

Discovery of MK-6096: A novel dual orexin receptor antagonist for the treatment of insomnia

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Prueksaritanont⁵; Joanne Stevens⁴; Pamela L. Tannenbaum⁴; Richard G. Bal⁶; Joyce Stellabott⁷; George D. Hartman¹; Christopher J. Winrow⁴; John J. Renger⁴. (1) Department of Medicinal Chemistry, Merck Research Laboratories, West Point PA 19486, United States (2) Department of Chemistry Modeling and Informatics, Merck Research Laboratories, West Point PA 19486, United States (3) Department of In Vitro Sciences, Merck Research Laboratories, West Point PA 19486, United States (4) Neuroscience Research, Merck Research Laboratories, West Point PA 19486, United States (5) Department of Drug Metabolism and Pharmacokinetics, Merck Research Laboratories, West Point PA 19486, United States (6) Department of Pharmaceutical Research and Development, Merck Research Laboratories, Rahway NJ 07065, United States (7) Department of Pharmaceutical Research and Development, Merck Research Laboratories, West Point PA 19486, United States

Orexin receptors are G-protein coupled receptors expressed within regions of the brain that govern the sleep-wake cycle through control of downstream pathways that involve histaminergic, dopaminergic, and cholinergic activity. Orexin receptors bind orexin A and B neuropeptides which are secreted by neurons projecting from the lateral hypothalamus. Genetic and pharmacological studies suggest orexin receptor antagonists could provide a novel therapy for treating insomnia and other disorders in which sleep/wake cycles are disrupted. The identification of potent orexin receptor antagonists is an active area of investigation and small molecule antagonists have entered late stage clinical development. We have recently disclosed the discovery of Suvorexant, a dual orexin receptor antagonist currently in Phase III studies. We have identified MK-6096, currently in Phase II clinical studies, as a potent dual orexin receptor antagonist (DORA) with significant in vivo sleep promoting efficacy in animals and humans. The structure of MK-6096 was optimized with respect to potency, pharmacokinetic profile, and physicochemical properties. Further, the team utilized computational modeling as well as small molecule X-ray diffraction studies to rationalize and confirm the preferred conformation for DORA's including MK-6096. The development and optimization of lead compounds along with the profile of clinical candidate MK-6096 will be presented.

MEDI 194

Rationale, design, and evaluation of isoform selective Hsp90 inhibitors: Progress towards Grp94 selective inhibition

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The 90 kDa heat shock proteins (Hsp90) are molecular chaperones that have rapidly evolved into promising therapeutic targets for the treatment of cancer. Recently, a new

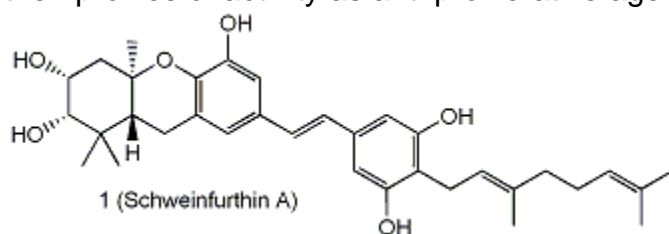
paradigm has emerged for Hsp90 inhibitors; the development of isoform selective inhibitors of Hsp90 that may avoid deleterious effects observed with current pan-Hsp90 inhibitors in clinical trials. However, studies directed toward the inhibition of individual isoforms have not been reported. The development of Hsp90 inhibitors that target one Hsp90 isoform offers a practical approach towards enhancing selectivity while improving toxicity profiles. In addition, isoform selective compounds will aid in elucidation of client proteins that each isoform is responsible for chaperoning. The development of isoform selective inhibitors has been hindered by the lack of concrete biochemical assays to characterize Hsp90 inhibitors selectivity profiles. The design, approach, and initial investigation of assays to identify Hsp90 isoform selective inhibitors are described.

MEDI 195

Schweinfurthins: Development of their antiproliferative activity

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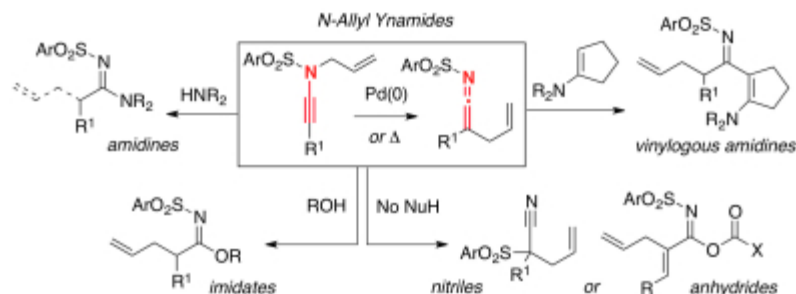
New chemotherapeutic agents are of greatest value when they attack a novel target because such activity can complement currently approved agents. The schweinfurthins are a family of potent natural products that appear to display a new mechanism of anti-proliferative activity. Because the natural source has provided only limited quantities of the schweinfurthins, we have undertaken a chemical synthesis of these natural products and employed a divergent strategy to prepare assorted congeners. Presented herein is the first total synthesis of schweinfurthin A (**1**), the synthesis of several analogues, and their profiles of activity as anti-proliferative agents.



MEDI 196

Exploration of novel rearrangements of *N*-allyl ynamides

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N-allyl ynamides have been found to undergo a novel Pd-catalyzed *N*-to-*C* allyl transfer through a Pd- π -allyl-ketenimine complex to form ketenimines *in situ*. Alternatively, a thermal 3-aza-Claisen rearrangement can furnish the same ketenimine intermediates, which followed by trapping with *N* and *O*-nucleophiles results in the *de novo* synthesis of α -allyl amidines, vinylogous amidines, and imidates. Without an external nucleophile present, an unexpected 1,3-sulfonyl shift can intercept the ketenimine intermediate, allowing access to quaternary nitriles. Similarly, a tandem aza-Claisen–[3,3]-sigmatropic rearrangement can be used to generate *a,b*-unsaturated mixed anhydrides with excellent control of the olefin geometry.

MEDI 197

Extrinsic recruitment of transcriptional coregulators by bifunctional nuclear receptor ligands

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Nuclear receptors (NR) are ligand-regulated transcription factors. They offer a means to directly affect the transcription of their target genes with small molecules, without simultaneous involvement of signaling cascades. This property underlies their success as drug targets. Transcriptional control is achieved through recruitment of transcriptional coregulators. The conformation of the receptor, which is modulated by ligand binding, determines which cofactors are recruited, and the effect is gene context dependent. Synthetic ligands are sought that can modulate receptors to yield desired expression patterns. Current strategies for ligand discovery are dependent on the intrinsically available receptor conformations, and we have thus developed a new strategy. We have shown that bifunctional molecules, made as conjugates of NR ligands to ligands of non-native transcription components, are able to recruit these targets to the NR and modulate transcription. This strategy holds promise to greatly expand the repertoire of the important class of NR targeting drugs

MEDI 198

Synthetic studies toward pladienolide B: A DNA splicing modulating antitumor agent

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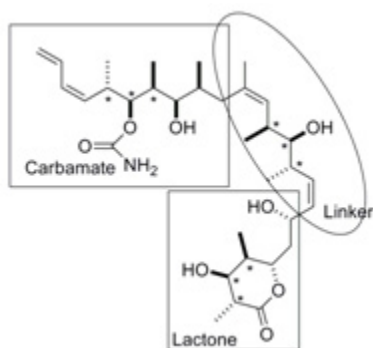
Recently, pladienolide B was isolated from an Okinawan strain of *Streptomyces platensis* and shown to possess an impressive antitumor activity against a range of drug resistant cancer cell lines. Subsequent biological studies have concluded its antitumor properties result from its unique ability to modulate DNA splicing activity resulting in the inhibition of cell growth. This presentation will showcase our recent efforts in developing a concise and efficient total synthesis of pladienolide B. Our convergent pathway utilizes a combination of readily available chiral synthons and asymmetric methodologies to synthesize pladienolide B with a high degree of stereoselectivity. In addition, our recent efforts to explore the molecule's key pharmacophoric features through the use of structural analogs will be briefly discussed.

MEDI 199

Synthesis of simplified discodermolide analogs

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Discodermolide (**1**) is a potent microtubule stabilizer, with actions more potent than paclitaxel. Pneumotoxiciates hindered its development in the clinical setting, and it is also of low abundance in nature, and must be synthesized from basic starting materials. Many analogs of discodermolide have been prepared. Simplifications to both the carbamate/diene and delta-lactone end regions of the molecule have been presented, but very few modifications to the linker region have been reported. Here we describe a new set of analogs in which the middle portion of discodermolide has been replaced with a *cis*-C=C bond, using olefin metathesis as the major coupling step. The analogs incorporate a variety of lactone and diene fragments, further expanding the structure activity relationship for discodermolide, and easing the total synthesis for this class of agents.



MEDI 200

Identification of a novel negative allosteric site on human $\alpha 4\beta 2$ and $\alpha 3\beta 4$ nicotinic acetylcholine receptors

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We determined the binding site of a class of nAChR negative allosteric modulators using computational methods, namely molecular dynamics and blind docking. Computationally-determined binding modes were validated by functional studies on mutant nAChRs. Based on the models, we hypothesized that T58K and F118V mutations on the β subunits would decrease the apparent affinity for the negative allosteric modulators compared to wild-type. Functional assays run on these mutant receptors yielded 7 and 10 fold decreases in efficacy for the T58K and F118V respectively, while leaving agonist activity unchanged. Calculated binding free energies to mutant homology models were found to be comparable to the functional data. The obstruction of a key loop's dynamics, similar to the mode of action of cobra toxin, is a hypothetical mode of antagonism and is supported by structural analysis and dynamics studies of models bound to these compounds.

MEDI 201

Chemistry at the chemistry-biology interface

Dale L. Boger, boger@scripps.edu. Department of Chemistry & the Skaggs Institute for Chemical Biology, The Scripps Research Institute, United States

Recent studies conducted at the chemistry-biology interface enlisting natural product leads (vancomycin, vinblastine), recently discovered endogenous signaling molecules (fatty acid amides) and structure-based drug design (FAAH inhibitors), and combinatorial chemistry targeting protein-protein and protein-DNA interactions will be detailed.

MEDI 202

Imaging tools to assess tissue selectivity

Thomas Krucker, thomas.krucker@novartis.com. Global Imaging Group, Novartis Institutes for BioMedical Research, Cambridge Massachusetts 02139, United States

Standard methods to determine tissue distribution combine radiolabeled compounds with whole body autoradiography or liquid scintillation counting of tissue homogenates.

Because of the terminal nature of these methods they require large numbers of individual samples if multiple time points are required and are limited to preclinical use. To overcome such limitations, and observe dynamic whole body biodistribution in animals and in patients, a series of in vivo imaging modalities, labeling technologies, and reporter systems may offer attractive alternatives. This presentation will provide a practical overview of the different imaging technologies and strategies that can be used to assess tissue targeting. Examples will be used to illustrate how in vivo and in situ imaging can be combined to investigate whole body, organ, and cellular biodistribution.

MEDI 203

Intestinal selective CCK-1 receptor agonists for the treatment of obesity

Kimberly O Cameron, *kimberly.o.cameron@pfizer.com*; Elena E Beretta; Yue Chen; Margaret Chu Moyer; Dilinie Fernando; Hua Gao; Jeffrey Kohrt; Sophie Lavergne; Angel Guzman-Perez; Christopher Hoth; Paul Da Silva Jardine; David A Perry; John R Hadcock; Denise Gautreau; Michael Makowski; Jana Polivkova; Lucy Rogers; Dennis O Scott; Andrew G Swick; Lucinda Thiede; Catherine E Trebino; Richard V Trilles; Julie Wilmowski; Yingxin Zhang; Janice E Chin; Richard Elliott; Amit Kalgutkar. Pfizer Global Research and Development, Groton CT 06340, United States

A number of drug targets are expressed within the small intestine. The ability to design compounds for these targets that selectively partition into the intestinal wall relative to the systemic circulation should enable both efficacy and safety. The cholecystikinin-1 receptor (CCK1R) is a potential target for the treatment of obesity and/or diabetes and is located primarily within the gastrointestinal tract. Studies suggest that activation of the CCK1R promotes a satiety effect via the vagal afferent neurons to the central nervous system. We recently disclosed the identification of a triazolobenzodiazepinone CCK1 receptor agonist, CE-326597, that demonstrated robust food intake effects in rodents with low systemic exposure. Our data suggest that the efficacy observed is primarily driven by intestinal exposure. We will present our approach for identification of a backup compound to CE-326597 which offered improved gut to plasma ratios and lower systemic exposure relative to CE-326597.

MEDI 204

Tissue selective antibody-drug conjugates

Gail D Lewis Phillips, *gdl@gene.com*. Department of Research Oncology, Genentech, Inc., South San Francisco CA 94080, United States

Antibody-drug conjugates (ADCs) exploit the antigen-selectivity of antibodies to deliver cytotoxic agents specifically to antigen-expressing tumor cells. Although the concept of utilizing antibodies for targeting cytotoxic drugs to tumors has existed for several decades, successes in clinical development have occurred only in the last several years due, in part, to advancements in linker technology and design of highly potent cytotoxic

agents. For most solid tumor antigens, differential expression between tumor and normal tissue is a key component for achieving both efficacy and safety. In contrast, antigen expression in hematologic tumors is often no different than expression in normal hematopoietic cells. However, efficacy can be achieved, with an acceptable safety profile, due to turnover and renewal of the normal hematopoietic cell population. Tolerability studies in rodents and cynomolgus monkeys provide insights into antigen-independent and –dependent toxicities. Efficacy and safety results for ADCs targeted to solid and hematologic tumors will be discussed.

MEDI 205

Designing for liver selective drug distribution: Hepatoselective glucokinase activators as a case study

Angel Guzman-Perez, *angel.guzman-perez@pfizer.com*; Jeffrey A Pfefferkorn; John Litchfield; Robert Aiello; Judith L Treadway; Martha L Minich; Kevin J Filipski; Christopher S Jones; Meihua Tu; Gary E Aspnes; Hud Risley; Stephen W Wright; Jian-Cheng Li; Jianwei Bian; John Benbow; Robert L Dow; Mary T Didiuk; Christian Perreault; Francis Bourbonais; David R Derksen; Margit MacDougall; Over Cabrera; James Landro; Karen Atkinson; Lili Yao; Rachel E Kosa; Nahor Haddish-Berhane; Bo Feng; David B Diugnan; Shenping Liu; Mark J Ammirati; John D Knafels. Pfizer Global Research and Development, Groton CT 06340, United States

The ability to target compounds to specific tissues offers the possibility of obtaining drugs with lower doses and improved safety. Targeting compounds to the liver is of particular interest in the metabolic disease area due to the key role played by this organ in glucose and lipid metabolism. For example, activation of glucokinase, the enzyme responsible for the conversion of glucose to glucose 6-phosphate, in the liver offers the potential for treating diabetes through increased hepatic glucose uptake and normalization of the elevated hepatic glucose output in these patients. Activation of glucokinase in the pancreas results in insulin secretion, which if excessive, increases the risk of hypoglycemia. We have identified a promising oral liver selective glucokinase activator. Herein we describe the medicinal chemistry strategy and specific design considerations used to target organic anion transporting polypeptides to achieve good liver selectivity with overall favorable ADME and PK properties.

MEDI 206

Selective androgen receptor modulators (SARMs): The discovery and development of tissue selective anabolic therapy

James T Dalton, *jdalton@gtxinc.com*; Duane D Miller; Ramesh Narayanan; Casey E Bohl; Domingo Rodriguez; K Gary Barnette; Mitchell S Steiner. GTx, Inc., Memphis TN 38163, United States

The therapeutic achievements of the selective estrogen receptor modulators have provoked an ever-expanding search for agents that modulate the actions of other nuclear hormone receptors. The goal of these selective nuclear receptor modulators is to maximize the beneficial therapeutic effects and minimize the unwanted clinical side effects of the natural hormone. Androgens are essential for muscle mass, bone mass, body composition, sebum production, hair growth, and lipid profiles in males and females, and prostate size in males. SARMs provide a promising alternative to existing anabolic therapies with advantages including receptor specificity, oral bioavailability, tissue selectivity, and toxicity profile. We used a battery of *in vitro* and *in vivo* systems to identify and develop a novel class of aryl propionamide SARMs that demonstrate potent, tissue selective pharmacologic activity. *In vitro* studies showed that SARMs bind with high affinity and specificity to AR, occupy a unique binding pocket, and elicit AR conformations that modulate distinct genomic and non-genomic signalling networks. Animal studies, a pivotal component of our screening paradigm, showed that they enhance muscle and bone mass and strength, while decreasing prostate size and exhibiting a wide safety margin. A Phase II clinical trial randomized 159 subjects diagnosed with either NSCLC, colorectal cancer, non-Hodgkin's lymphoma, chronic lymphocytic leukemia or breast cancer to receive GTx-024 or placebo daily for 16 weeks. GTx-024 exhibited tissue selectivity with beneficial effects on lean body mass (muscle) and physical function with no changes in measurements for serum PSA (prostate), sebum production (skin and hair), or serum LH (pituitary) compared to placebo, supporting its advancement to Phase III clinical trials. Combined, the preclinical and clinical data for the aryl propionamide SARMs provide compelling evidence of their tissue selectivity and therapeutic promise for the prevention and treatment of muscle wasting.

MEDI 207

Diverse modes of efficacy and stimulus bias of allosteric modulators of GPCRs

P. Jeffrey Conn, jeff.conn@vanderbilt.edu. Department of Pharmacology, Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University, Nashville TN, United States

Allosteric modulators of GPCRs provide a novel approach to modulation of specific GPCR subtypes. Negative allosteric modulators (NAMs) inhibit whereas positive allosteric modulators (PAMs) potentiate responses to endogenous agonists. Allosteric modulators offer high selectivity for targeted receptors and provide an exciting new approach to development of novel therapeutic agents. Allosteric modulators of the metabotropic glutamate receptor mGluR5 provide an excellent example of the multiple modes of efficacy and diverse actions that can be achieved with allosteric modulators of GPCRs. Both PAMs and NAMs for mGluR5 have been advanced as drug candidates and have robust effects in animal models that predict efficacy in treatment of CNS disorders. The diversity of allosteric modulators now available is allowing us to develop fundamental new insights into the multiple mechanisms by which these compounds

regulate GPCR function and are providing new insights into the functional impact of different modes of efficacy of allosteric modulators.

MEDI 208

Exploiting intracellular domains to create peptide GPCR modulators

Thomas J McMurry, *tcmurphy@anchortx.com. Research and Development, Anchor Therapeutics, Cambridge Massachusetts 02142, United States*

Pepducins comprise a short peptide derived from the sequence of a G-protein coupled receptor (GPCR) intracellular loop linked to a hydrophobic membrane anchor. This breakthrough technology can be readily applied to orphan receptors as well as validated targets and results in compounds that modulate GPCR activity via a unique allosteric mechanism. The talk will focus on the discovery of CXCR4-targeted pepducin agonists, their structure activity relationships and DMPK characteristics.

MEDI 209

Lead optimization of a selective M1 muscarinic receptor positive allosteric modulator

Scott D Kuduk¹, *scott_d_kuduk@merck.com*; **Ronald K Chang**¹; **Christina N Di Marco**¹; **William J Ray**²; **Lei Ma**²; **Marion Wittmann**²; **Matthew A Seager**²; **Kenneth A Koeplinger**³; **Charles D Thompson**³; **George D Hartman**¹; **Mark T Bilodeau**¹. (1) Department of Medicinal Chemistry, Merck & Co., West Point PA 19438, United States (2) Department of Alzheimer's Research, Merck & Co., West Point PA 19438, United States (3) Department of Drug Metabolism, Merck & Co., West Point PA 19438, United States

Identification of new mechanisms to treat the neurodegenerative effects of Alzheimer's disease (AD) represents a major unmet medical need. One approach to ameliorate the cognitive decline in AD has been to target the neurons of the basal forebrain cholinergic system via activation of the M₁ muscarinic receptor. Non-selective M₁ muscarinic agonists have previously shown positive cognitive effects on in AD patients, but were limited due to cholinergic adverse events thought to be mediated by activation of the M₂ to M₅ sub-types. One strategy to confer selectivity for M₁ is to identify a positive allosteric modulator, which would target an allosteric site on the M₁ receptor rather than the highly conserved orthosteric acetylcholine binding site. HTS lead quinolone carboxylic acid BQCA evolved into a highly selective Quinolizidinone carboxylic acid M₁ positive allosteric modulator with good pharmacokinetic and in vivo properties. This presentation will focus on the lessons experienced during allosteric modulator lead optimization toward identification leading to a compound with enhanced CNS exposure and improved efficacy in a rodent in vivo model of cognition for further pre-clinical evaluation.

MEDI 210

Allosteric modulators of the A₃ adenosine receptor

Kenneth A Jacobson¹, *kajacobs@helix.nih.gov*; **Adriaan P IJzerman**²; **John A Auchampach**³; **Zhan-Guo Gao**¹. (1) Laboratory of Bioorganic Chemistry, NIDDK, National Institutes of Health, Bethesda MD 20892-0810, United States (2) Leiden/Amsterdam Center for Drug Research, Leiden University, Leiden 2300RA, The Netherlands (3) Department of Pharmacology, Medical College of Wisconsin, Milwaukee WI 53226, United States

A₃ adenosine receptor (AR) agonists are of interest for treatment of ischemia, inflammation, and cancer. Screening of known antagonists identified positive allosteric modulators (PAMs) that enhance agonism of endogenous adenosine and inosine. A 3-(2-pyridinyl)isoquinoline (VUF5455) has distinct SAR in allosteric and orthosteric (presumed from the competitive displacement of orthosteric radioligands) binding to A₃AR. Docking model of VUF5455 in agonist-occupied A₃AR proposed its binding near the extracellular loops. Allosteric, but not orthosteric binding of imidazoquinolinamines required N274 in TM7. *N*-(3,4-Dichlorophenyl)-2-cyclohexyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (LUF6000) increased agonist efficacy (cAMP inhibition and agonist-induced GTPγS binding) without affecting agonist potency. LUF6000 converted a potent nucleoside-derived A₃ neutral antagonist MRS542, but not diverse heterocyclic A₃ antagonists, into full agonist. Scission of the imidazole ring led to 2,4-disubstituted quinoline PAMs. Species dependence of LUF6000 indicated robust A₃ PAM action in human and dog but not rat, mouse, and rabbit, and cardioprotective action is being explored.

MEDI 211

Lu AF21934: A brain-penetrant mGlu4 positive allosteric modulator tool compound

Dario Doller, *dado@lundbeck.com*. Chemical & Pharmacokinetic Sciences, Lundbeck Research USA, Paramus NJ 07652, United States

Basal ganglia (BG) circuitry understanding and the unmet medical need in the treatment of motor disorders in Parkinson's disease (PD) has led many groups to the investigation of glutamate receptor modulation. A decade of research has provided strong support for the potential impact of mGlu4 receptor potentiation in restoring a balance to BG circuitry in PD. We have implemented a strong coalition with academic and private collaborators, and explored the pharmacology associated with potentiation of the mGlu4 receptor via a novel biochemical mechanism (positive allosteric modulation), utilizing a brain-penetrant tool compound, Lu AF21934. This presentation will highlight aspects of the medicinal chemistry, mechanistic and behavioral pharmacology of our efforts, as well as exemplify the potential of open collaboration between the pharmaceutical industry and academic and private centers of expertise.

MEDI 212

Positive allosteric modulation of the mGluR5 receptor: SAR, SPR and in vivo activity of ADX47273 derivatives

Jean-Philippe Rocher¹, jean-philippe.rocher@addexpharma.com; Giovanni Palombi²; Stefania Gagliardi²; Béatrice Bonnet¹; Emmanuel Le Poul¹; Anne-Sophie Bessis¹; Sonia Poli¹; Mark Epping-Jordan¹; Bernard Lüdwig¹; Robert Lütjens¹; Vincent Mutel¹. (1) Addex Pharmaceuticals S.A., Plan-les-Ouates Geneva 1228, Switzerland (2) Nikem Research S.r.l., Baranzate Milano 20021, Italy

Allosteric modulators of mGluR₁₋₈ have been shown to offer a valid strategy to develop non amino-acid like therapeutics that can be administered orally and that readily cross the blood-brain barrier. In addition, positive allosteric modulators (PAMs) are unlikely to induce a rapid desensitization such as the currently available agonists. mGluR5 receptors are located mainly on post-synaptic elements in the brain (cortex, thalamus, hippocampus and cerebellum), from where they regulate the activity of NMDA & AMPA, as well as the excitability of the post-synaptic neurons. mGluR5 PAMs have emerged as a novel class of compounds for the treatment of neuropsychiatric disorders. The aryl-oxadiazole ADX47273 has been the topic of intense interest for the pharmacological evaluation of the mGluR5 PAM approach; this compound demonstrated promising antipsychotic activity in preclinical rodent models for positive symptoms of schizophrenia and it was also active in cognition models. ADX47273 has opened an avenue to a novel class of drug-like molecules in this field. We will present the multiparametric lead optimization program which led to the identification of several chemical series of highly selective mGluR5 receptor PAMs. Compared to ADX47273 which suffered of a poor bioavailability; the new molecules are systematically active in rodent behavioral models.

MEDI 213

Evolving ecosystem of pharmaceutical research and development

Ralph E Christoffersen, RChris@Morgenthaler.com. Partner and Head, Life Sciences Team, Morgenthaler Ventures, Boulder CO 80303, United States

Over several decades, the ecosystem that feeds R&D leading to new biotechnology and pharmaceutical advances has changed tremendously. During this time, the cost of developing new biomedical products has grown nearly ten-fold while productivity dropped by a factor of two. Fortunately, some government incentives enlivened academic and nonprofit discovery efforts, and venture capital and philanthropy began to play major roles in early stage and then later stage product development. Today, a powerful matrix of innovation involving venture capital, governmental labs, private philanthropy, pharmaceutical and medical device companies is evident throughout this ecosystem, and efforts are underway to develop translational interfaces to help address many challenges – financial, regulatory, otherwise – in moving ideas through the hurdles to ultimately reach the market. This talk will examine the current status of these

efforts from the perspective of someone who has experience in each of the sectors (academia, large pharma, biotech and venture capital investing).

MEDI 214

Shortening the pipeline between academia and the private sector

Regis B. Kelly, *Regis.Kelly@qb3.org*; Douglas Crawford. California Institute for Quantitative Biosciences (QB3), United States

Although academia is funded by NIH “to enhance the Nation's economic well being” (NIH Mission Statement) the enhancement step is usually not ideal. Recently universities have created institutions that interface between their scientists and technology transfer offices with the goal of speeding up the commercialization of academic research. These interface institutions provide mentorship, pre-commercial funding or incubator space, all of which can de-risk research while still in an academic setting, making it more attractive for licensing or spin-offs. Key challenges for such institutions are to know what industry needs, which innovations could be disruptive and what is attractive to angel or venture investors. Surprisingly, big pharma seems to be as interested in academic spin-outs as in research within academia, thus leading to the idea of a bioinnovation ecosystem. QB3 has partnered with Deloitte to evaluate the advantages and challenges of such an ecosystem – results of their analysis will be presented.

MEDI 215

Drug discovery successes in nonprofits and biotech/pharma collaborations

P. Jeffrey Conn, *jeff.conn@Vanderbilt.edu*. Department of Pharmacology, Vanderbilt Center for Neuroscience Drug Discovery, United States

Scientists in academic settings have made tremendous advances in understanding human disease but often fail to make critical links that allow this information to be useful in industry settings. Likewise, fiscal pressures make it increasingly difficult for companies to invest in basic research needed to translate these discoveries into marketable products. The Vanderbilt Center for Neuroscience Drug Discovery (VCNDD) invests in early stage drug discovery with a goal of de-risking investment in innovative approaches to treatment of serious brain disorders in industry settings. Approximately 100 VCNDD scientists work in a focused team fashion to advance novel target validation, lead discovery, and lead optimization for generation of quality clinical candidates. These efforts are now generating a steady pipeline of drug candidates and represent multiple approaches to partnering with large pharmaceutical companies, small companies, foundations, and NIH in an effort to help develop new sustainable models for early stage drug discovery.

MEDI 216

Academic approaches to address drug discovery challenges: The Moulder Center for Drug Discovery Research at Temple University

Magid Abou-Gharbia, *magid.abougharbia@temple.edu. The Moulder Center for Drug Discovery Research at Temple University, United States*

The pharmaceutical industry is currently facing enormous challenges, such as reduced efficiencies, declining innovation and the industry's perceived tarnished image. There is a clear need for change in the paradigms designed to address these challenges. While Pharma have embarked on a range of initiatives, other sectors have also responded. The NIH recently announced a new, internally-funded drug discovery initiative. Several academic drug discovery centers have also recently been established to facilitate the transition of innovative academic ideas and breakthroughs into attractive drug discovery opportunities. The Moulder Center, a multidisciplinary research hub and integrated drug discovery unit, was recently founded at Temple University with this very mission in mind. The presentation will highlight current challenges facing the pharmaceutical industry and the Moulder Center's capabilities and approaches to providing academic and biotech researchers with a drug discovery perspective to their biomedical research. Results from a Stimulus Challenge Grant-funded project will be highlighted.

MEDI 217

Drug discovery and development at Southern Research Institute

John A. Secrist III, *secrist@southernresearch.org. Southern Research Institute, United States*

Southern Research Institute has been involved in the discovery of new drugs, mainly for cancer, for over 50 years. As a not-for-profit organization with no endowment, we have relied on external sources of support for our existence, a fact that has made our drug discovery efforts a significant challenge. Financial support for our core businesses has been obtained competitively from the federal government, as well as from commercial organizations. Additionally, our internal drug discovery efforts have been advanced through reinvestment of our own funds (from IP revenues on recently approved drugs). Clearly, challenges have included maintaining state of the art equipment and facilities, as well as recruiting scientists with the talents needed to carry out effective discovery research. This presentation will provide information about our history, operational challenges and how we met them, and drug discovery accomplishments over the years as well as present our current activities.

MEDI 218

Cancer stem cells: Concepts, definitions and clinical relevance

William Matsui, *matsuwi@jhmi.edu. Division of Hematologic Malignancies, The Sidney Kimmel Comprehensive Canc. Ctr at John Hopkins, Baltimore MD 21287, United States*

Cancer stem cells (CSCs) have been identified in an ever-increasing number of human malignancies. Although initial studies primarily focused on the enhanced tumorigenicity and self-renewal potential of CSCs, emerging data have demonstrated that they are also relatively drug resistant and highly invasive and migratory. Thus, CSCs may play a broad role in clinical oncology that encompasses disease initiation, relapse, and progression. Despite these findings, major challenges remain including demonstrating that CSCs are clinically relevant, developing potential targeting strategies, and identifying the optimal clinical settings to evaluate efficacy. These translational barriers will be discussed in greater depth

MEDI 219

Quantitative phosphoproteomic analysis of the STAT3/IL-6/HIF1 α signaling network: An initial study in GSC11 glioblastoma stem cells

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GSC11 glioma stem cell responses to perturbations in the IL-6/STAT3/HIF1 α loop were explored by treatment with a JAK2/STAT3 phosphorylation inhibitor, IL-6 and hypoxia. Over 3,000 proteins were identified in the study, which employed phosphoprotein and phosphopeptide enrichment, chemical tagging, and tandem mass spectrometry. Multiple comparisons between the sample conditions yielded expected changes and novel insights into the contribution of each factor to the cancer stem cell response. Taken together with a glycolipidomic/transcriptomic study of GSC11, we report the most complete systems biology study of cancer stem cell differentiation to date. Enhanced understanding may help to discover novel therapeutic approaches that target cancer stem cells

MEDI 220

Glioma-associated cancer-initiating cells induce immunosuppression

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Glioblastoma multiforme (GBM) has a dismal survival and cancer-initiating cells have been shown to recapitulate the characteristic features of GBM including mediating chemotherapy and radiation resistance. We isolated cancer-initiating cells from GBM patients and found that they inhibited T cell proliferation and activation, induced regulatory T cells, triggered T cell apoptosis and recruit and polarize the M Φ s/microglia to become immunosuppressive (M2). The immunosuppressive properties were reversed

when STAT3 is blocked. In mice that co-express PDGF-B + *Bcl-2* or STAT3 under the control of the glioneuronal-specific *Nestin* promoter, the high-grade gliomas that develop had a marked intratumoral influx of macrophages influenced by tumor STAT3 expression and were a negative prognosticator. In mice with gliomas treated with the STAT3 blockade agent, WP1066, there was a marked increase in survival time. Blockade of the STAT3 pathway with agents such as WP1066 would be a compelling approach for treating malignant gliomas

MEDI 221

Wnt signaling in stem cells and cancer stem cells: A tale of two coactivators

Michael Kahn, *kahnm@usc.edu*. Dept. of Biochemistry, University of Southern California, Los Angeles CA 90033, United States

Wnt signaling pathways play divergent roles during development, normal homeostasis and disease. Until recently, a rationale for the dichotomous behavior of Wnt/beta-catenin signaling in controlling both proliferation and differentiation has been unclear. We have developed a model to explain the divergent activities of Wnt/beta-catenin signaling. Our model highlights the distinct and non-redundant roles of the coactivators CBP and p300 in the Wnt/beta-catenin signaling cascade. The critical feature of the model is that CBP/catenin-mediated transcription is critical for proliferation and stem cell/progenitor cell maintenance; whereas p300/catenin mediated transcription leads to the initiation of a differentiation program. Both basic research on differential coactivator usage in stem cell (both normal and cancer) populations and the 'bench to bedside' translation of this work into the development of PRI-724, the first in man CBP/catenin antagonist will be discussed.

MEDI 222

Rationale for Smo inhibition as therapeutic intervention in minimal residual disease

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Although many cancers respond to initial therapy at rates well above 50%, relapse rates are very high, resulting in poor long term survival. One theory for the high rate of relapse is the persistence of malignant cells at minimally detectable levels, known as minimal residual disease (MRD). IPI-926 is a small molecule that antagonizes the Hh pathway by inhibiting Smoothened (Smo) and is currently being evaluated in clinical trials. In preclinical models of MRD, administration of IPI-926 significantly delayed time to tumor relapse. Overall, these findings suggest that Hh pathway-dependent "progenitor cells" may contribute to the high relapse rates seen in patients following standard therapies. The rationale for evaluation of Smo inhibitors in the setting of MRD following administration of chemo or targeted therapies will be provided

MEDI 223

Catalyzing opportunities in translational research

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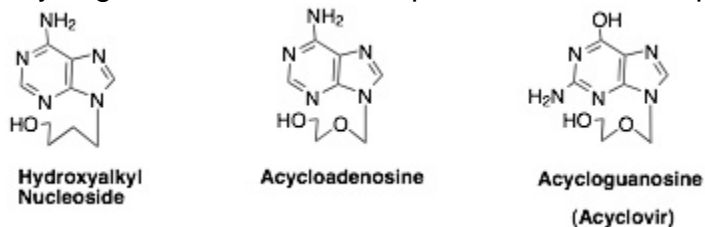
NIH has a strong tradition of fueling the development of new approaches for treating disease. According to a recent *New England Journal of Medicine* study, more than 20% of innovative drugs approved by the FDA from 1990-2007 were discovered by NIH-supported researchers. Yet, many conditions, especially rare and neglected diseases, still lack effective therapeutics. One problem is that the development pipeline currently contains many bottlenecks that reduce efficiency and increase costs. To advance the discipline of translational science, NIH has announced plans to create a new center to study the various steps of drug development, identify constriction points that may be amenable to re-engineering, and experiment with innovative methods to streamline the process. In this lecture, the NIH Director will discuss the rationale for establishing the National Center for Advancing Translational Sciences, and describe how its activities will benefit a wide range of stakeholders.

MEDI 224

Acyclonucleosides to Ziagen: A journey

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In 1971, the first acyclonucleoside, acycloadenosine, was reported from our lab in which the sugar of a nucleoside was replaced with a 2-hydroxyethoxymethyl moiety. Our acycloadenosine was subsequently submitted for testing at Burroughs Wellcome Company by my Ph.D. advisor, Howard J. Schaeffer, and was found to have significant anti-herpes activity. The adenine was then exchanged with guanine and the subsequent acycloguanosine was developed into the anti-herpes drug, Acyclovir.



In 1987, our first carbocyclic 2',3'-dideoxy-2',3'-didehydro 2-amino-6-substituted purine nucleoside analogs, called "carbovirs", were submitted to NIH and were the most active cpds found in their new HIV assay after AZT. After a long process, abacavir emerged as the candidate for development. Abacavir was approved by the FDA on December 18, 1998 under the trade name Ziagen[®], and as a triple combination with zidovudine and

lamivudine (Trizivir^R), and as a double combination with lamivudine (Kivexa^R/Epzicom^R) by GSK.



MEDI 225

SAHA: The past, present, and future of its special mode of action

Ronald Breslow, *rb33@columbia.edu. Department of Chemistry, Columbia University, United States*

Some years ago Dr. Paul Marks and the Breslow lab entered into a collaboration that ultimately led to the invention of SAHA, an approved anticancer drug that is now marketed by Merck under the name Zolanza. It had a completely new mode of action, and was the first drug approved in this class, although now many companies and medical scientists are pursuing related compounds with the new target. In this lecture I will briefly review the history of its invention, and recent progress in derivatives of SAHA with important selectivities, including work now underway in the current Breslow/Marks collaboration.

MEDI 226

Discovery of the antitumor drug ALIMTATM

Edward C. Taylor, *etaylor@princeton.edu. Department of Chemistry, Princeton University, United States*

Cofactors derived from folic acid play key roles in a host of diverse metabolic reactions essential for the formation of DNA, RNA, and some amino acids and proteins. Our initial search for inhibitors of folate-dependent enzymes first led to the discovery that (6R)-5,10-dideaza-5,6,7,8-tetrahydrofolic acid (lometrexol) blocked de novo purine biosynthesis and exhibited excellent therapeutic activity against a variety of solid tumors. Subsequent investigations, pursued through a remarkable collaboration between Princeton University and Eli Lilly & Co., culminated in the discovery of a new oncolytic agent, AlimtaTM (pemetrexed disodium). This lecture will describe how Alimta was discovered, its current clinical status, and our understanding of its unique mode of action.

MEDI 227

Bridging the gap between basic science and the clinic: An emerging role for drug discovery in an academic medical center campus

Milton Brown, *mb544@georgetown.edu. Georgetown University Medical Center, United States*

The gap between academic basic science and clinical translation continues to stall and challenge U.S. medical centers. However, without strong synthetic medicinal chemistry support, academic medical centers remain inept at advancing drug discovery opportunities. We will address the impact, obstacles and challenges of implanting medicinal chemistry support and building a successful academic drug discovery and development program on an academic medical center campus. We will identify creative ways of engaging academic medical centers towards developing productive partnerships and unlocking leveraged resources. The model includes the opportunity for early vetting of risky projects, strategies to cultivate and harnessing innovative and disruptive science, early development of an industrial champion with implantation of an industrial scientist in academic residence and opportunities for developing innovative proof of concept studies. Discussion will be provided on the impact of embedding drug discovery into an academic medical center to support translational research and to activate productive academic pharmaceutical partnerships towards developing new and impactful medicines.

MEDI 228

Metabolomic and network-flux approaches to evaluate and identify high-impact targets in cancer

Edward M. Driggers, *edward.driggers@agios.com; Kevin M. Marks; Abhishek Jha; Shalini Sethumadhavan; Marie C. Keenan; Collin Hill; Hin-Koon Woo; Andrew N. Tyler. Agio Pharmaceuticals Inc., United States*

Metabolic function is an output of not only metabolite levels, but also (and perhaps principally) pathway flux. Consequently, methods to evaluate and compare network-level flux patterns have inherent value in interrogating the metabolic state of cells. We have developed a metabolomic analysis platform that a) enables the generation of multiple metabolic networks for modeling, b) enables characterization of flux in those networks through kinetic flux analysis of time-course data from isotopically labeled metabolite pools via LCMS, and c) enables sensitivity analysis of the flux models to network topology. We will present the capabilities of this approach in the context of examining cell lines that carry metabolic alterations that result in the production of modified metabolomics signatures and/or flux patterns. These alterations include somatic mutations in enzymes, or amplifications of enzyme encoding genomic regions that alter expression levels, both of which can be tightly associated with specific tumor types (eg. IDH-2 mutations linked strongly to acute myelogenous leukemia (AML)).

MEDI 229

Cancer metabolism, HIF-1, and novel anticancer therapies

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Increased glucose uptake and metabolism is a universal characteristic of advanced solid cancers. There are two well-established mechanisms underlying the reprogramming of tumor metabolism. First, intratumoral hypoxia induces the activity of the transcriptional activator hypoxia-inducible factor 1 (HIF-1) by inhibiting the O₂-dependent prolyl and asparaginyl hydroxylases that inhibit HIF-1 α stability and transactivation, respectively. Second, genetic alterations increase the activity of HIF-1, MYC, and other transcription factors that increase the expression of glucose transporters (GLUT1, GLUT3), glycolytic enzymes (ALDOA, ENO1, HK2, LDHA, PKM2), pH regulators (CA9, NHE1, MCT4), and proteins that inhibit mitochondrial metabolism (BNIP3, PDK1). Metabolites, such as the glycolytic end-product lactate, also induce HIF-1 activity, thereby providing a signal to further increase glycolytic metabolism. We have identified a novel feed-forward mechanism by which glycolytic enzyme expression leads to increased HIF-1 transcriptional activity. This pathway may be designed to increase HIF-1 activity under non-hypoxic conditions and may be of importance in cancers where genetic alterations increase HIF-1 α expression in an O₂-independent manner. We have also demonstrated that daily administration of digoxin (and other cardiac glycosides), acriflavine, or low-dose doxorubicin (and other anthracyclines) blocks tumor growth and inhibits HIF-1 activity by blocking HIF-1 α synthesis, HIF-1 α :HIF-1 β dimerization, and HIF-1 DNA binding, respectively.

MEDI 230

Identification of lactate dehydrogenase A inhibitors using fragment-based lead generation

Richard A. Ward, *richard.a.ward@astrazeneca.com; Jon Winter; Chris De Savi; Ryan Greenwood; Stuart Pearson; Alice Hooper; Kin Tam; Alison Hunter; Clare Lane; Julie Tucker; Clare Brassington; Alessandro Caputo; Martin Vogtherr; Martin Watson; Geoff Holdgate; Gareth Davies; Jonathan Tart; Jonathan Wingfield; Louise Goodwin; Nicky Whalley; Susan Critchlow; Kevin Hudson. AstraZeneca, United Kingdom*

Lactate Dehydrogenase A (LDHA) catalyses the conversion of pyruvate to lactate, utilising NADH as a co-factor. It has been identified as an important target in the area of cancer metabolism. We shall present our progress using Fragment-Based Lead Generation, assisted by x-ray crystallography to develop small molecule LDHA inhibitors. Fragment hits were identified by NMR screening and optimised into lead compounds with nano-molar binding affinities measured by Biacore, with binding modes elucidated by x-ray structure. Finally, we shall summarise their modification into cellular active compounds for target validation work.

MEDI 231

Mapping dysregulated metabolic pathways in cancer using activity-based proteomics

Daniel K Nomura, *DNomura@scripps.edu*; Benjamin F Cravatt. Department of Chemical Physiology, The Scripps Research Institute, La Jolla CA 92037, United States

Tumor cells display progressive changes in metabolism that correlate with malignancy, including development of a lipogenic phenotype. How stored fats are liberated and remodeled to support cancer pathogenesis, however, remains unknown. Here, we show that the enzyme monoacylglycerol lipase (MAGL) is highly expressed in aggressive human cancer cells and primary tumors, where it regulates a fatty acid network enriched in oncogenic signaling lipids that promotes migration, invasion, survival, and *in vivo* tumor growth. Overexpression of MAGL in non-aggressive cancer cells recapitulates this fatty acid network and increases their pathogenicity -- phenotypes that are reversed by a MAGL inhibitor. Interestingly, impairments in MAGL-dependent tumor growth are rescued by a high-fat diet, indicating that exogenous sources of fatty acids can contribute to malignancy in cancers lacking MAGL activity. Together, these findings reveal how cancer cells can co-opt a lipolytic enzyme to translate their lipogenic state into an array of pro-tumorigenic signals. We also show that MAGL expression and the expression of several other metabolic enzymes correlate with EMT and cancer stem cell markers across a broad panel of human cancer cell lines. These data point to a set of metabolic enzymes and pathways, such as the MAGL-endocannabinoid/fatty acid network, that may create key biochemical changes in cancer cells that support their progression to a high-malignancy state. Disrupting these pathways with small-molecule inhibitors, as we show with MAGL and its cognate inhibitor JZL184 in this study, could impair tumor cell pathogenicity and offer novel ways to treat the most aggressive forms of cancer.

MEDI 232

Modulation of pyruvate kinase activity and its role in cell metabolism

Matthew G. Vander Heiden, *mvh@mit.edu*. Koch Institute for Integrative Cancer Research at MIT and the Dana Farber Cancer Institute, United States

Genetic driver events in cancer activate signaling pathways that alter cell metabolism, and clinical evidence has linked metabolism with cancer outcomes. Together, this has raised interest in targeting metabolic enzymes for cancer therapy. The best strategy to target cancer metabolism, however, remains unclear. Cancer cells exhibit altered metabolism to efficiently incorporate nutrients into biomass to support proliferation. The M2 isoform of pyruvate kinase (PK-M2) promotes anabolic metabolism and is selected for optimal tumor growth *in vivo*. Paradoxically, the ability of PK-M2 to promote anabolic metabolism is associated with decreased pyruvate kinase enzyme activity, and genetically engineered mouse cancer models support the notion that loss of pyruvate

kinase activity favors tumor growth. Nevertheless, the ability to reactivate pyruvate kinase may also be important for some tumor cells. These findings suggest that pyruvate kinase activity modulation may be a strategy to target cancer. Results from studies using small molecule activators of PK-M2 to restore the high pyruvate kinase activity found in most normal tissues will be presented. How these and associated studies inform efforts to target glucose metabolism for cancer therapy will also be discussed.

MEDI 233

Discovery, development, and utility of activators of the human M2 isoform of pyruvate kinase

Craig J. Thomas¹, craigt@mail.nih.gov; Matthew B. Boxer¹; Jian-kang Jiang¹; Matthew G. Vander Heiden^{2, 3, 4}; Martin J. Walsh¹; Kyle Brimacombe¹; Min Shen¹; Amanda P. Skoumbourdis¹; Hee Won Park^{5, 6}; Lewis C. Cantley^{3, 7}; Douglas S. Auld¹. (1) NIH Chemical Genomics Center, National Human Genome Research Institute, United States (2) Dana Farber Cancer Institute, United States (3) Department of Systems Biology, Harvard Medical School, United States (4) David H. Koch Institute for Integrative Cancer Research at MIT, United States (5) Structural Genomics Consortium, University of Toronto, Canada (6) Department of Pharmacology, University of Toronto, Canada (7) Division of Signal Transduction, Beth Israel Deaconess Medical Center, United States

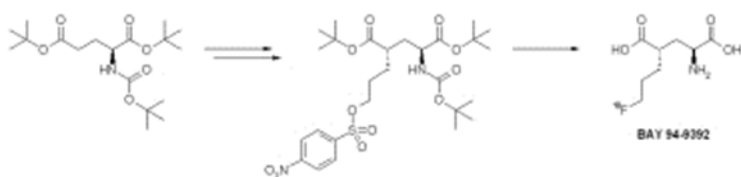
Pyruvate kinase (PK) is a critical metabolic enzyme operating at the ultimate step in glycolysis. In humans there are two pyruvate kinase genes and each produces two distinct gene products by alternative splicing. Following embryonic development, adult tissues switch to either PK-M1 or the tissue specific L or R isozymes. However, in cancerous cell lines revert entirely to the M2 isoform. Rapidly proliferating cells (including embryonic and cancer cells) require elevated levels of molecular building blocks, many of which are the products of glycolysis. Mechanistically the M2 isoform requires activation by fructose-1,6-bis phosphate (FBP) and it has been demonstrated that oncogenic phosphotyrosine peptides can bind the M2 isoform in a manner that displaces FBP and effectively down-regulates PK-M2 activity. Down-regulation of PKM2 is suggested to allow diversion of glycolytic intermediates towards nucleotide and lipid biosynthesis. Taken together these studies imply a therapeutic strategy where activation of PKM2 can potentially restore normal cellular metabolism. We describe here the identification and optimization and utility of several small molecule activators of human PKM2.

MEDI 234

Synthesis and preclinical evaluation of BAY 94-9392: A novel PET tracer for tumor specific imaging

Heribert Schmitt-Willich, heribert.schmitt-willich@bayer.com; Mathias Berndt; Matthias Friebe; Norman Koglin; Andre Mueller; Volker Gekeler; Ludger M. Dinkelborg. Bayer Healthcare Pharmaceuticals, Germany

Positron Emission Tomography (PET) tracers targeting adaptations of the inter-mediary tumor metabolism possess the potential to be highly specific tumor imaging agents. 4-[F-18]Fluoro-L-glutamate (BAY 85-8050) was shown to accumulate in tumors.¹ However, *in vivo* defluorination in cancer patients limits its use as a viable alternative to FDG ([F-18]-Fluorodeoxyglucose).² In this study, several novel F-19 and [F-18] L-glutamate derivatives were synthesized and investigated in cell competition assays to characterize the responsible transporter and to analyze the tolerated conformational space. (4S)-(3-[F-18]fluoropropyl)-L-glutamate (BAY 94-9392) was selected as the most promising candidate. Stereospecific precursor synthesis and radiolabeling have been optimized and the resulting F-18 labeled tracer was characterized in several *in vitro* and *in vivo* tumor models comprising transporter-selective knock-down cells. Tracer uptake competition studies demonstrated specific transport of BAY 94-9392 via the cystine/glutamate exchanger (xCT, SLC7A11). No metabolites were observed. PET imaging with excellent tumor visualization and high tumor to background ratios was achieved in preclinical tumor models. In addition, in contrast to FDG, BAY 94-9392 did not accumulate in inflammatory lesions. Both preclinical and clinical studies are in progress for further characterization.



MEDI 235

Putting cancer on a diet: Targeting fatty acid biosynthesis

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In the 1920s, Otto Warburg observed that cancer cells have a voracious appetite for glucose and produce lactic acid even in the presence of ample oxygen. This is due to an increase in glycolysis and a decrease in oxidative phosphorylation. More recently it has become clear that additional metabolic pathways are deregulated in cancer, notably the activation of anabolic pathways including amino acid and pentose phosphate production, and increased fatty acid biosynthesis. For cancer drug discovery the challenge is to identify the exact metabolic pathways and nodes on which cancer cells rely, intersecting this with targets whose inhibition can be tolerated by normal cells. Fatty acid synthase (FAS) meets these criteria and is a novel lipid metabolism target for oncology. FAS is the only human enzyme that synthesises the 16 carbon fatty acid palmitate from acetyl-CoA and malonyl-CoA. The gene encoding this enzyme is

amplified in cancer cells, the protein over-expressed and dramatic increases in fatty acid production have been observed in human tumours. In contrast to normal cells, cancer cells rely on *de novo* synthesis of palmitate rather than sourcing this fatty acid from the diet. Inhibition of FAS in cancer cells by potent and selective small molecule inhibitors decreases phospholipid synthesis and increases the levels of malonyl-CoA. *In vitro* the inhibition of FAS increases PARP cleavage and causes a G2 arrest of cancer cells. *In vivo* the inhibition of FAS is effective in the treatment of subcutaneous tumour xenografts.

MEDI 236

Huntington's disease: Biology, therapeutic strategies, and translational challenges

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Huntington Disease (HD) is a dominantly inherited neurodegenerative disorder that results from expansion of the poly-glutamine repeat in the Huntingtin (HTT) gene. There are currently no effective treatments for this devastating disease. Given its monogenic nature, disease modification therapies for HD should be theoretically feasible. Currently, pharmacological therapies aimed at disease modification by altering levels of HTT protein are in late-stage preclinical development. In addition, based on our current understanding of HTT function and the main pathological mechanisms identified as central to HD progression, we have advanced the identification and development of novel small molecule drugs with potential utility in HD. At the CHDI Foundation we are evaluating novel small molecule therapeutics based on their ability to affect the following mechanisms: basal ganglia synaptic dysfunction, autophagy and bioenergetics. During this presentation, I will also review existing genetic models of HD, current biomarker and translational efforts both for measuring disease progression as it is relevant to disease modification trials, as well as to the modulation of disease-relevant mechanisms.

MEDI 237

Assessing HD biology: Biomarkers

Michael Orth, michael.orth@chdifoundation.org. Department of Biology, CHDI Foundation Inc., Los Angeles CA 90046, United States

Huntington disease is a neurodegenerative disorder caused by a CAG repeat expansions mutation in the huntington gene. There is currently no causal treatment, while symptomatic treatment can improve quality of life HD is invariably incapacitating, and eventually fatal, with motor, cognitive and behavioral problems. The development of novel therapeutics is a major quest in HD. Once available they need to be evaluated carefully. This requires reliable assessment tools. In addition, future therapeutics, and thus clinical trials with them, may focus on particular sub-groups of patients or specific

pathways. Thus, biomarkers are needed that serve at least these purposes in that they are 1) An indicator of the biological state of HD 2) They can be objectively measured and evaluated reflecting a change of normal biological processes, or HD specific pathogenic processes, 3) They measure pharmacologic responses to a therapeutic intervention. In HD, the candidates for biomarkers include the clinical measurement of the phenotype, e.g. motor signs, using rating scales, imaging the brain including magnetic resonance imaging and other parameters that can be measured in easily accessible body fluids or tissues. There may not be a single biomarker, or set of markers, for all stages of HD, and there may be yet other markers for the purpose of inclusion of patients into trials and the assessment of the effects of therapeutics targeting specific pathways. To date, imaging the brain seems most promising; however, the cost of scanning and the great care required for data quality when comparing results obtained in different scanners call for complementary and simpler markers for instance in blood or cerebro-spinal fluid. There is hope that the large scale efforts under way will go some way to meet this challenge.

MEDI 238

Discovery of brain penetrant JNK3 inhibitors as potential therapeutics for the treatment of Huntington's disease

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c-Jun NH2-terminal kinases (JNKs) are members of the MAP kinase family that are primarily activated by cytokines and exposure to environmental stress. JNK3 is the isoform primarily expressed in brain, where it phosphorylates the N-terminal transactivation domain of c-Jun, resulting in enhancement of c-Jun dependent transcriptional events. JNK3 has been implicated as a therapeutic target in various neurodegenerative disorders, including Huntington's disease, where it is believed to play a regulatory role in the signaling pathways during neuronal apoptosis. It has been shown that inhibition of JNK3 leads to beneficial effects in various models of neurodegeneration. Our goal is to identify brain penetrant proof of concept tools for in vivo validation of JNK3 as a therapeutic target for the treatment of Huntington's disease. CHDI's strategy is to benchmark literature JNK3 inhibitors as potential tools, while working to develop promising hits from virtual screening into potent, brain penetrant JNK3 inhibitors. CHDI has begun collaborations with AMRI to establish the necessary biochemical and cellular assays to support a medicinal chemistry program, and with BioFocus to enable structural biology support of CADD. This presentation will provide

an update on the status of our program, including the challenges met and the path forward in our goal towards proof of concept and a potential therapeutic for Huntington's disease.

MEDI 239

Advances in the development of selective brain penetrant KMO inhibitors as potential treatment for Huntington's disease

Leticia M Toledo-Sherman¹, *leticia.toledo-sherman@chdifoundation.org*; Michael Prime²; Dirk Winkler³; Maria Beconi¹; Fred Brookfield²; Chris Brown²; Stephen Courtney²; Andreas Ebner³; Rachel Grigg²; Estelle Hamelin-Flegg²; Peter Johnson²; Volker Mack³; Richard Marston²; William Mitchell²; Paula Pena²; Laura Reed²; Selvaratnam Suganthan²; Ignacio Munoz-Sanjuan⁴; Eric Schaeffer⁴; Derek Weddell²; Naomi Went²; Christin Winkler³; John Wityak¹; Christopher Yarnold²; Celia Dominguez¹.
(1) Medicinal Chemistry, CHDI Foundation Inc, Los Angeles CA 90045, United States
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Dysregulation of the kynurenine pathway has been implicated in a variety of central nervous systems disorders, including Huntington's Disease. Several metabolites of kynurenine catabolism are bioactive and can modulate both synaptic and inflammatory processes in adult tissues. In particular, kynurenic acid (KYNA) can act as a neuroprotective agent through its weak antagonistic activity at the NMDA receptor; in addition, KYNA has been shown to modulate synaptic glutamate release and cholinergic signaling, activities which might be of relevance to HD pathophysiology. Other kynurenine metabolites, 3-hydroxy-kynurenine (3HK), and quinolinic acid (QA), have been shown to be neurotoxic in vitro and in vivo. In early stage HD patients as well as in the R6.2 model of HD, 3HK levels are elevated in a region-specific manner. The enzyme which catalyzes the conversion of kynurenine to 3HK is Kynurenine mono-oxygenase (KMO). CHDI, in collaboration with Evotec, has identified and optimized a series of selective inhibitors of KMO. The presentation will cover the status of the program, and describe the challenges associated with the development of brain penetrant molecules that display adequate pharmacokinetic properties for in vivo efficacy testing in HD animal models.

MEDI 240

Selective HDAC class IIa inhibitors as potential therapeutics for Huntington's disease

Roland Burli¹, *roland.burli@glpg.com*; Celia Dominguez². (1) Department of Medicinal Chemistry, BioFocus, Saffron Walden Essex CB10 1XL, United Kingdom (2) Department of Medicinal Chemistry, CHDI Foundation, Los Angeles California 90045, United States

Huntington's disease (HD) is a genetic, neurodegenerative disorder that causes abnormal muscle coordination and leads to cognitive decline, dementia and premature death. HDAC4 is one of eleven metal-dependent histone deacetylase isoforms (HDACs) and has been recognized as a potential target for HD. The target validation is based on the finding that heterozygous knock down of the HDAC4 gene in R6/2 mice (disease model) resulted in a partially restored phenotype (personal communication, Professor Gill Bates, King's College London). As HDAC4 adopts multiple biological functions, the critical question remains whether blockage of its catalytic site will be sufficient to replicate the knockdown data. To determine this, we developed HDAC4 inhibitors with excellent cell-based activity and isoform selectivity. Progress toward an *in vivo* proof-of-concept study will be reported, which includes PK/PD readouts in brain and muscle tissue as well as optimization of the inhibitors for *in vitro* ADME and *in vivo* pharmacokinetic properties.

MEDI 241

Design of selective phosphodiesterase inhibitors and their potential utility for the treatment of Huntington's disease

Patrick R Verhoest, *patrick.r.verhoest@pfizer.com*. Neuroscience Medicinal Chemistry, Pfizer, Groton CT 06371, United States

Phosphodiesterase inhibitors have shown proven utility as therapeutics in multiple diseases by inhibiting the hydrolysis of specific pools of cyclic nucleotides. Pfizer has invested heavily in identifying and advancing selective inhibitors for multiple PDEs into clinical trials. The neuroscience group through structure based drug design and parallel chemistry enablement have identified a PDE10 (PF-2545920) and a PDE9 (PF-4447943) inhibitor that have advanced into phase 2 clinical testing. These compounds have appropriate pharmacokinetics in humans and exhibit clear central target engagement. As part of an effort to identify alternative indications, a collaboration was developed with CHDI. Through internal work and at CHDI, PDE10 and PDE9 inhibitors have shown potential utility for the treatment of Huntington's Disease (HD). PDE10 inhibitors have been shown to improve behavioral measurements and prolong survival in the R6/2 transgenic mice. Multiple PDE inhibitors have shown positive outcomes in electrophysiology measurements including improving LTP in R6/2 brain slices. In this presentation, the phase 1 human data, preclinical HD efficacy data and medicinal chemistry strategy will be disclosed.

MEDI 242

Discovery of TAK-441, a pyrrolo[3, 2-c]pyridine derivative: A highly potent and orally active investigational hedgehog signaling inhibitor

Satoshi Sasaki¹, *Sasaki_Satoshi@takeda.co.jp*; Tomohiro Ohashi¹; Yuya Oguro¹; Toshio Tanaka¹; Zenyu Shiokawa¹; Nobuhiro Fujii²; Sachio Shibata¹; Yoshihiko Sato¹; Yoji Sagiya¹; Hiroko Yamakawa¹; Harumi Hattori¹; Maki Miyamoto²; Shigeru Kondo²;

Yoshimasa Ishimura²; Hideaki Tojo²; Atsuo Baba¹. (1) Pharmaceutical Research Division, Takeda Pharmaceutical Co., Ltd., Tsukuba Ibaraki 3004293, Japan (2) Pharmaceutical Research Division, Takeda Pharmaceutical Co., Ltd., Osaka Osaka 5328686, Japan

The Hedgehog (Hh) signaling pathway plays an important role in cell growth and differentiation during embryonic development and is activated in several types of cancer. It therefore represents an attractive anti-cancer therapeutic target and several Hh signal inhibitors are currently being assessed in clinical trials. High throughput screening of our compound library identified several inhibitors of Hh signaling. Subsequent efforts to improve the pharmacokinetic profile of these compounds led to discovery of the investigational agent TAK-441, a novel pyrrolo[3,2-c]pyridine-4-one derivative. TAK-441 potently inhibited Hh signaling *in vitro* in a Gli reporter assay (IC_{50} = 4.4 nM) and also demonstrated an excellent pharmacokinetic profile (mouse cassette dose, 10 mg/kg; AUC_{0-8h} 28.35 μ gh/mL). Oral administration of TAK-441 (25 mg/kg once daily) completely inhibited tumor growth in a mouse medulloblastoma allograft model without significant toxicity. In this presentation, we will describe the design and biological evaluation of TAK-441 and related compounds.

MEDI 243

Novel pyrido[2,3-b]pyrazines as orally active ERK inhibitors

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A common feature of many deregulated molecular lesions in cancer is the activation of the RAS - Raf - MEK - ERK signal transduction pathway (hereafter referred to as the ERK pathway). This pathway controls a number of fundamental cellular process including cell survival, proliferation, motility and differentiation. It is constitutively activated in cancers of the lung, colon, pancreas, kidney, and ovary. ERK is pivotal in the pathway downstream of RAS, Raf and MEK, acting as central point where multiple signaling pathways coalesce to drive transcription. Here we present the structure class of pyrido[2,3-b]pyrazines, which has been identified as novel, potent, orally active inhibitors for ERK. The poster describes our efforts during a medicinal chemistry program supported by X-ray crystallography and molecular modeling towards the optimization of pyrido[2,3-b]pyrazines as novel series of ERK inhibitors. So far, compounds with activity values in the low nanomolar range have been identified. The synthesis, structure-activity relationships, physicochemical data and ADME parameter, as well as encouraging *in vivo* data of this structure class are presented. In summary, we designed a series of novel, potent inhibitors of ERK kinase by starting with a submicromolar lead compound 1 (**D-89220**), followed by several optimization cycles within a structure-guided medicinal chemistry program. This optimization led amongst others to the identification of the compound **AEZS-131**, which is currently under *in vivo* evaluation.

MEDI 244

Synthesis and SAR studies of colchicine binding site tubulin inhibitors as potent and orally bioavailable anticancer agents

Yan Lu¹, *lu_yane@hotmail.com*; Chien-Ming Li²; Zhao Wang¹; Jianjun Chen¹; Wei Li¹; James T Dalton²; Duane D Miller¹; Wang Jin¹. (1) University of Tennessee, Health Science Center, United States (2) GTX Inc., United States

A series of phenyl amino thiazoles (PAT) was designed and synthesized in an effort to develop promising anti-cancer agents. We obtained PAT derivatives from modifications of 4-substituted methoxybenzoyl-aryl-thiazoles (SMART) by introducing an NH linkage between the A and B rings. The antiproliferative activity of PAT agents against melanoma and prostate cancer cell lines was evaluated and structure-activity relationships were developed. The PAT template maintained nano molar (nM) range potency against cancer cell lines via inhibiting tubulin polymerization, was not susceptible to P-glycoprotein mediated multidrug resistance *in vitro*, and markedly improved solubility and bioavailability compared with the SMART template. This data suggested that these new synthesized amino linked compounds have appropriate potency and PK profiles to be developed as a new class of orally bioavailable antitubulin agents. Synthesis, SAR and biological evaluation of the SMART agents will be presented.

MEDI 245

Photoimmunotherapeutic nanoparticles: Combination therapy for metastatic breast cancer

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Photoimmunotherapy (PIT) is a promising field for cancer treatment that combines the phototoxic and immune-stimulating ability of photodynamic therapy (PDT) with the widespread effectiveness of the immune system. We speculate that co-delivery of an immunostimulant with a photosensitizer using a nanoparticle delivery platform will be a useful means to attack metastatic cancer. To investigate this, we have initiated the construction of new PIT agents using a hybrid nanoparticulate delivery platform for the treatment of late-stage breast cancer. Briefly, we encapsulated a photosensitizer within a polymeric nanoparticle core made up of poly(D,L-lactic-co-glycolic acid)-*b*-poly(ethylene glycol) (PLGA-*b*-PEG). After coating the outside of the polymeric core with gold nanoparticles, we further modified the gold surface with CpG-ODN, a single-stranded DNA that is a known immunostimulant. Synthesis, PDT activity, and immune stimulatory effects of these constructs will be presented.

MEDI 246

7-Azaindenoisoquinolines: Topoisomerase I inhibitors with improved water solubility

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A series of 7-azaindenoisoquinoline topoisomerase I (Top1) inhibitors have been prepared to investigate the effect of increased electron deficiency of the aromatic system on the ability to stabilize Top1-DNA cleavage complex. Ab initio calculations suggest that introduction of the nitrogen into the aromatic system of indenoisoquinolines would facilitate charge transfer complex formation with DNA, thus improving the π - π stacking interactions. The present study shows that 7-azaindenoisoquinolines demonstrate substantially improved water solubility without decrease in the Top1 inhibitory activity or cytotoxicity. Analysis of the results of biological evaluation revealed that some lactam ring substituents enable intercalation into free DNA whereas others only allow binding to the Top1-DNA cleavage complex.

MEDI 247

Synthesis and evaluation of novel androgen receptor inhibitors: Potential candidates for castrate-resistant prostate cancer treatment

Sanjay V. Malhotra¹, malhotrasa@mail.nih.gov; Vineet Kumar¹; Yeong Sang Kim²; Sunmin Lee²; Jane Trepef². (1) Laboratory of Synthetic Chemistry, SAIC-Frederick, Inc., National Cancer Institute at Frederick, Frederick Maryland 21702, United States (2) Medical Oncology Branch, CCR,, National Cancer Institute, Bethesda Maryland 20892, United States

Growing new cases of prostate cancer in United States and worldwide, have warranted an urgent need for more effective therapy against prostate cancer. Castrate-resistant prostate cancer (CRPC) represents progression from androgen-dependent to androgen-independent disease, which makes Androgen receptor (AR) an important target in CRPC. We have synthesized a series of benzylideneacetophenone based compounds and shown their activity in the inhibition of androgen receptors. An extensive structure-activity relationship (SAR) was performed on a systematically designed library of this scaffold for impact on PSA gene expression. The hit compounds were treated with LNCaP cells and the inhibition of AR target genes PSA, TMPRSS2 (androgen and AR dependent genes) and UBE2C (androgen independent, AR dependent genes) was determined. Also, these studies have identified small molecules that inhibit AR target gene expression significantly in 22Rv1 a prostate cancer cell line, in which PSA expression is insensitive to FDA-approved drug bicalutamide. **Acknowledgement:** This

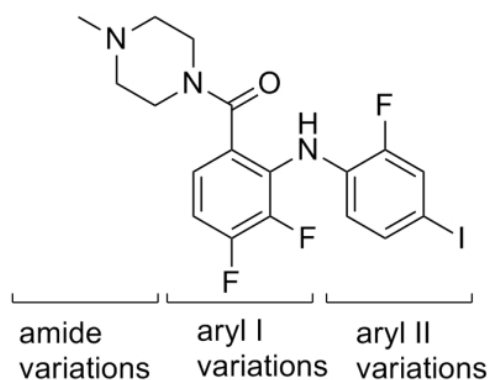
Project has been funded with federal funds from the National Cancer Institute, NIH under contract No. HSN261200800001E

MEDI 248

Ortho-amido diphenylamines as MEK5 inhibitors

Suravi Chakrabarty¹, chakrabartys@duq.edu; **Patrick T. Flaherty**¹; **Darlene Monlish**²; **Jane Cavanaugh**²; **Sankar G. Manepalli**³; **Jeffrey D. Madura**³. (1) Mylan School of Pharmacy, Department of Medicinal Chemistry, Duquesne University, Pittsburgh PA 15282, United States (2) Mylan School of Pharmacy, Department of Pharmacology, Duquesne University, Pittsburgh PA 15282, United States (3) Bayer School of Natural and Environmental Sciences, Duquesne University, Pittsburgh PA 15282, United States

The mitogen activated protein kinase (MAPK) pathway mediates intracellular responses to extracellular events. It mediates significant cellular events including embryogenesis, cell differentiation, cell proliferation, and cell death. Phosphorylation of unique isoforms of ERK (Extracellular signal-Regulated Kinases) by its complementary kinase (MEK) is the most selective event in the MAPK signaling cascade. ERK5 is the only known substrate of MEK5. MEK5 mediated generation of pERK5 is initiated by binding of an extracellular mitogen or ligand, activation of MEKK2 or MEKK3, and then subsequent formation of catalytically active pMEK5. MEK5 and pERK5 are significantly up regulated in specific tumor types including breast and prostate cancers. A series of diphenylamines were designed based on a homology model of MEK5 based on the X-ray crystal structure of MEK1 (PDB ID: 3EQC) and the MEK5 selective inhibitor shown below. The design, modeling, synthesis, and testing of amide and aryl variations will be presented.



MEDI 249

Syntheses and antitumor activity of *N*-hydroxyethyl-4-azadidehydropodophyllotoxin derivatives

Ajay Kumar¹, drajaybhati@gmail.com; **Vineet Kumar**²; **Antonio E. Alegria**¹; **Sanjay V. Malhotra**². (1) Department of Chemistry, University of Puerto Rico at Humacao,

Humacao Puerto Rico 00791, United States (2) Laboratory of Synthetic Chemistry, SAIC-Frederick, Inc., National Cancer Institute at Frederick, Frederick Maryland 21702, United States

Podophyllotoxin (**PPT**) has been known to possess anti-tumor activity. Derivatives of podophyllotoxin, namely etoposide, etopophos and teniposide have been developed for the treatment of a variety of malignancies. However, due to the drug resistance developed by cancer cells as well as side effects associated with the use of these agents in clinic, the search for new effective anticancer analogues of podophyllotoxin remains an intense area of research. The structural complexity of podophyllotoxin, arising from the presence of four stereogenic carbons in ring C has restricted most of the structural activity relationship (SAR) studied by derivatization of the parent natural product rather than by *de novo* multi-step chemical synthesis. Our endeavor in this field lead to synthesis of a library of *N*-hydroxy aza-podophyllotoxin derivatives, which were screened for their antitumor activity using the National Cancer Institute's 60 human tumor cell line screen. This was followed by a screen of *in vivo* activity using a panel of tumor hollow-grafts implanted in mice consisting of breast (MDA-MB-231), non-small lung (NCI-H23 and NCI-H522), colon (SW-620 and COLO 205), melanoma (UACC-62, MDA-MB-435 and LOXIMVI), ovarian (OVCAR-5 and OVCAR-3) and CNS (U251 and SF-295) cell lines. This is the first report of aza-podophyllotoxins anticancer activity evaluation on such a broad panel of cancer cell lines. The toxicity of all the active compounds was low, while their antiproliferative activity was high, providing a wide therapeutic window for their potential application as anticancer drugs.

Acknowledgement: This Project has been funded with federal funds from the National Cancer Institute, NIH under contract No. HSN261200800001E

MEDI 250

Structure-based design of urea and methylurea inhibitors of B-Raf^{V600E}: The development of highly potent and efficacious inhibitors

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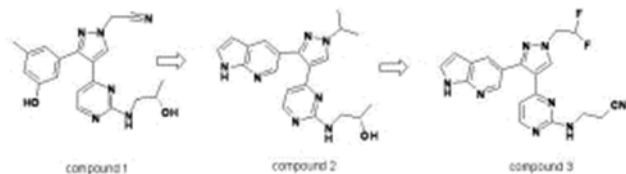
The V-600 mutation of B-Raf kinase results in constitutive activation of the MAPK signal pathway and is present in nearly 8% of all solid tumors and particularly prevalent in melanoma. Using structure-based design, we herein report a novel series of urea and methylurea inhibitors of B-Raf^{V600E} demonstrating high enzyme and cell potency. This presentation will also detail *in vitro* and *in vivo* efficacy and pharmacokinetic profiles of this new class of B-Raf inhibitors.

MEDI 251

Discovery of potent, selective inhibitors of mutant B-Raf

Cynthia L Palmer, cindy.palmer@pfizer.com; Jingrong Cui; Judith Deal; Danlin Gu; Chuangxing Guo; Susan Kephart; Maria A Linton; Indrawan McAlpine; Mason Pairish; Shubha Bagrodia; Yixue Cao; Shinji Yamazaki; Dorothy DeLisle; Annette John-Baptiste. Pfizer Worldwide Research and Development, San Diego California 92121, United States

Discovery of potent, selective inhibitors of mutant B-Raf Cynthia L. Palmer, Jingrong Cui, Judith Deal, Danlin Gu, Chuangxing Guo, Susan Kephart, Maria A. Linton, Indrawan McAlpine, Mason Pairish, Shubha Bagrodia, Yixue Cao, Shinji Yamazaki, Dorothy DeLisle, Annette John-Baptiste B-Raf is mutated in a number of human cancers including melanoma, thyroid and colorectal. Raf is a key kinase in the Ras/Raf/Mek pathway, thus making mutant B-Raf an attractive oncology target. Discussed herein is the medicinal chemistry effort done at Pfizer directed at developing a potent mutant B-Raf inhibitor starting from a potent phenol-pyrazole lead, (2-(3-(3-hydroxy-5-methylphenyl)-4-(2-((S)-2-hydroxypropylamino)pyrimidin-4-yl)-1H-pyrazol-1-yl)acetonitrile (compound 1). As common to phenolic compounds, secondary metabolism, especially glucuronidation, resulted in poor PK properties. Investigation of phenol replacements led to the identification of hit azaindole, (2S)-1-(4-(1-isopropyl-3-(1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ol (compound 2). Also presented is the optimization of the hit azaindole to give compound 3 which not only demonstrated improved ADME properties, but also excellent kinase selectivity and efficacy in animal TGI studies.



MEDI 252

Discovery of potent selective B-Raf^{V600E} kinase inhibitors

Judith Deal, judy.deal@pfizer.com; Cynthia Palmer; Jingrong Cui; Danlin Gu; Chuangxing Guo; Susan Kephart; Maria Linton; Tami Marrone; Indrawan McAlpine; Michele McTigue; Mason Pairish; Scott Sutton; Dorothy DeLisle; Kristina Rafidi; Evan Smith; Shinji Yamazaki; Xiao-Hong Yu; Shubha Bagrodia. Pfizer Worldwide Research and Development, San Diego CA 92121, United States

The discovery of selective potent B-Raf^{V600E} kinase inhibitors is described. Kinase counter-screening of file compounds led to a phenol, 3-bromo-5-(4-pyridin-4-yl-1H-pyrazol-3-yl)phenol, which showed moderate B-Raf^{V600E} potency and attractive ligand efficiency. The phenol series was optimized to improve potency but had consistently poor PK properties. Several heterocycles were successfully identified to replace the

phenol head group. Further optimization led to potent, selective B-Raf^{V600E} kinase inhibitors with good pharmaceutical properties and in vivo efficacy.

MEDI 253

Evaluation of glycosidated ginsenoside mimics as anticancer agents

Sanjay V. Malhotra, *malhotrasa@mail.nih.gov*; **Ian Jamie Talisman**, *Laboratory of Synthetic Chemistry, SAIC-Frederick, Inc., National Cancer Institute, Frederick Maryland 21702, United States*

Ginsenosides are active components of the ginseng plant, which has been frequently used as a traditional herbal medicine for weakness and fatigue. More recently, it has been evaluated for various disease states including diabetes, Parkinson's disease, and cancer. Over thirty different ginsenosides, comprised of a steroid core of 17 carbon atoms arranged in a 6,6,6,5 ring system, have been isolated from ginseng. Ginsenosides exhibit a range of anticancer activities depending on the carbohydrate substitution pattern of the core. However, the complexity of the core makes medicinal chemistry efforts to systematically vary the carbohydrate portion of these molecules difficult. We have designed a series of glycosylated ginsenoside mimics to reduce the size of the core and facilitate structure activity relationship evaluation. Herein, we report the synthesis of a small library of ginseng saponin mimics. On evaluation, several of these compounds were shown to inhibit growth and/or target pathways implicated in the progression of certain cancers. Results of these studies will be presented.

Acknowledgement: This Project has been funded with federal funds from the National Cancer Institute, NIH under contract No. HSN261200800001E

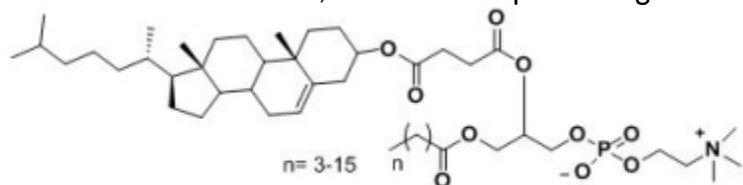
MEDI 254

Improved cisplatin efficacy using sterol modified liposomes

Heidi M Kieler-Ferguson¹, *kieler@berkeley.edu*; **Jean M Fréchet**¹; **Francis C Szoka Jr.**². (1) *Department of Chemistry, University of California-Berkeley, Berkeley CA 94720-1460, United States* (2) *Department of Bioengineering and Therapeutic Science, University of California-San Francisco, San Francisco CA 94143, United States*

Cisplatin, a widely used chemotherapeutic, suffers from severe toxicity. Attempts to circumvent this toxicity through liposomal encapsulation have yielded liposomes incapable of cisplatin release or with complicated formulations, not amenable for clinical use. Utilizing a new class of sterol modified lipids (SML), we investigated lipid anisotropy and acyl chain length effect on cisplatin leakage. SML-liposomes with shorter acyl chain lengths provided better cisplatin release, higher *in vitro* toxicities, and easier

formulation conditions, with several promising candidates for *in vivo* studies.



NIH GM061851 & EB003008

MEDI 255

Synthesis and cytotoxicity of cisplatin analogs against oncogenic cells

Van Vo, vanv@unlv.nevada.edu; *Ontida Tanthmanatham; Haesook Han; Pradip K. Bhowmik; Bryan L. Spangelo. Department of Chemistry, University of Nevada, Las Vegas, Las Vegas Nevada 89154, United States*

Cisplatin belongs to a family of platinum-containing compounds used in the treatment of various cancers. While quite effective, its application is limited. In hope of discovering more suitable compounds, a series of cisplatin analogues of the formula (4,4'-bis[R]-2,2'-bipyridine)PtCl₂ [where, R = varying alkoxy groups] were synthesized. The antitumor activities of these compounds were examined in a lung cancer cell line (A549) using the MTS cell proliferation assay. Three compounds, where R = -O(CH₂)₂CH₃ (EC₅₀ = 36±4 μM), -O(CH₂)₃CH₃ (EC₅₀ = 24±2 μM), -O(CH₂)₄CH₃ (EC₅₀ = 43±1 μM), were found to be more effective than cisplatin (had no effect, even up to 1 mM concentration) after a one hour treatment. Similar results were obtained when compound R = -O(CH₂)₃CH₃ was tested on several other cancer cell lines. These results demonstrate the potential utilization of these compounds as chemotherapeutic drugs and warrant further investigation to determine its mechanism of action.

MEDI 256

Semisynthetic parthenolide analogs: Chemical probes of biological function and new anticancer agents

Daniel A Harki, daharki@umn.edu; *Dan Wang; Joseph K Hexum; F A Meece. Department of Medicinal Chemistry, University of Minnesota, Minneapolis MN 55414, United States*

Parthenolide (PTL) is a plant-derived natural product from feverfew (*Tanacetum parthenium*) and a well-established active component of many natural medicines. The anti-inflammatory properties of PTL have been reported in scores of scientific publications, resulting in its evaluation as a therapeutic for leukemia, breast cancer, prostate cancer, and pancreatic cancer. Additionally, PTL has been shown to selectively kill acute myelogenous leukemia stem cells without destroying normal hematopoietic

stem cells, and this finding has generated excitement in the drug discovery community. Notably, cancer stem cells are highly resistant to chemotherapeutic drugs and treatment regimens that allow cancer stem cells to survive may ultimately result in disease relapse. Our laboratory has synthesized a number of PTL analogues to (I) elucidate the mechanism of action of this compound and (II) to optimize the potency and pharmacokinetic parameters of PTL. Our progress in both areas will be presented.

MEDI 257

Application of ProTide technology to gemcitabine: A successful approach to overcome key cancer resistance mechanism

Magdalena Slusarczyk, *slusarczykm1@cf.ac.uk*; Christopher McGuigan. Welsh School of Pharmacy, Cardiff University, Cardiff Wales CF10 3NB, United Kingdom

A family of gemcitabine prodrugs carrying a phosphoramidate moiety was synthesized and biologically evaluated for anti-cancer activity on different tumor cell lines. These compounds were obtained by applying the ProTide technology to gemcitabine using phosphorochloridate chemistry. Among all synthesized molecules bearing various aryl, amino acids and ester moieties, the L-Alanine series exhibited good anti-cancer activity in the *in vitro* experiments. In particular one compound (**NUC-1031**) was recognized to be more potent in pancreatic cell lines (Mia-Pa-Ca-2, Bx-PC-3) than gemcitabine. On the basis of its favourable *in vitro* data, the effect of our lead compound on tumor growth in the nude mouse xenograft models was examined. **NUC-1031** showed statistically significant reduction in pancreatic tumor volume versus the parent molecule and control. Hence, a Phase I/II study utilising **NUC-1031** is planned. Data suggest that **NUC-1031** may bypass and overcome the key limitations associated with parent gemcitabine's clinical effectiveness.

MEDI 258

⁶⁴Cu-TE2A-NCS-trastuzumab as a potential PET radiotracer for tumors expressing Her2/neu receptor: Synthesis, radiolabeling, and in vivo studies

Ajit V. Dale¹, *ajitvdale@gmail.com*; Darpan N. Pandya¹; Jung Y. Kim²; Yeong S. Ha¹; Gwang I. An²; Jeongsoo Yoo¹. (1) Department of Molecular/Nuclear Medicine, Kyungpook National University, Daegu 700-422, Republic of Korea (2) Molecular Imaging Research Center, Korea Institute of Radiological and Medical Sciences, Seoul 139-706, Republic of Korea

New bifunctional chelate, which holds Cu(II) ions firmly and also makes facile conjugation with antibodies, is an essential component for the successful development of ⁶⁴Cu-immunoconjugates. Here we report new synthesis of TE2A-NCS and demonstrate its usefulness as a potential bifunctional chelate. TE2A-NCS was synthesized from cyclam in seven steps with 58% overall yield. Then, it was easily conjugated to the trastuzumab antibody via its NCS functional group. The conjugate

TE2A-NCS-trastuzumab was labeled in 94% radiolabeling yield within 10 min at 30°C. After purification, the radiochemical purity was greater than 99%. When ^{64}Cu -TE2A-NCS-trastuzumab was injected into nude mice bearing NIH3T6.7 tumor xenografts, tumor was clearly visualized with high signal to background ratio at 1 and 2 days. Biodistribution data was also well matched with microPET data. All our data demonstrate high potential of TE2A-NCS as a promising bifunctional chelator.

MEDI 259

Synthesis of a folate targeted camptothecin prodrug using a monodisperse PEG spacer

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The folate receptor (FR) has emerged as an attractive target for selective delivery of folate coupled therapeutic agents. We describe the construction and assessment of a folate conjugate synthesized using a monodisperse, Fmoc protected PEG building block. The PEG spacer serves to ensure water solubility and optimal ligand-receptor interaction. Assembly was achieved using Fmoc solid phase synthesis to build a folate PEG cysteinyl construct, which was further reacted with pyridyldithioethyl carbonate camptothecin. The conjugate demonstrated an IC₅₀ value of approximately 6 nM in an FR+ KB cancer cell line, and its activity was blocked when assessed in the presence of a 1000 fold excess of free folic acid. Moreover, the conjugate yielded a relative binding affinity and serum binding comparable to previously synthesized constructs with peptide spacers. Together, these studies demonstrate the utility of newly available, monodisperse, Fmoc PEG building blocks for the synthesis of targeted therapeutic agents.

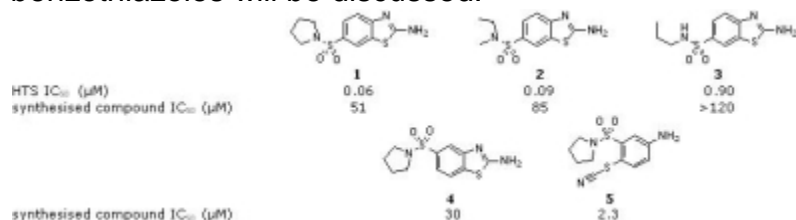
MEDI 260

Development of substituted benzothiazoles as ERK5 inhibitors

Ruth H Bawn¹, *R.H.Taylor@ncl.ac.uk*; Bernard T Golding¹; Roger J Griffin¹; Tim Hammonds²; Hing Leung³; David Newell¹; Laurent Rigoreau²; Ai Ching Wong²; Celine Cano¹; Ian R Hardcastle¹. (1) Department of Chemistry, Newcastle Cancer Centre at the Northern Institute for Cancer Research, Newcastle upon Tyne Tyne and Wear NE1 7RU, United Kingdom (2) Discovery Laboratories, Cancer Research Technology, London WC1E 6BT, United Kingdom (3) Department of Cancer Sciences and Molecular Pathology, The Beatson Institute for Cancer Research, Glasgow University, Glasgow G61 1BD, United Kingdom

Deregulated ERK5 signalling is linked to cancer, including prostate cancer.¹ Small molecule ERK5 inhibitors may be effective cancer therapies.² Benzothiazoles were identified as hits in an ERK5 high-throughput screen (IC₅₀s = 60-900 nM). Examples **1-3** were resynthesised but were inactive. The 5-sulfonamido isomers **4** showed modest

activity. Thiocyanatobenzene **5** showed activity. SARs of additional substituted benzothiazoles will be discussed.



MEDI 261

Computational assessment of the potential role of chalcogenated flavonoids as antioxidants, enzyme inhibitors and cell signalling modulators via computational analysis

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Flavonoids have been studied for decades due to their putative health-promoting effects, initially attributed to their antioxidant capacity as H-atom donors and, more recently, to their ability to modulate cell signalling pathways. We have synthesized sulfur and selenium-containing derivatives of chrysin and quercetin, and evaluated their potential antioxidant activity both experimentally, by assessing their capacity to reduce the DPPH radical, and by using computational methods to probe the energetics of the various mechanisms contributing to their antioxidant activity. Their role as signal modulators has been surveyed by computational docking of the various derivatives to key proteins, including CYPs and various kinases involved in signalling. The role of these compounds as potential modulators of signalling-dependent carcinogenic pathways is discussed in terms of their interactions with protein residues and inhibition constants.

MEDI 262

Metallocene derivatives as selective estrogen receptor modulators a computational docking to estrogen receptors α and β

M Matilde Marques, matilde.marques@ist.utl.pt; **Gonçalo C Justino**; **Shrika G Harjivan**. Centro de Química Estrutural, Instituto Superior Técnico, Lisbon - 1049-001, Portugal

Organometallic moieties have been frequently incorporated in known drugs aiming to improve their therapeutic properties. Raloxifene, a benzo[b]thiophene derivative, is a selective estrogen receptor (ER) modulator (SERM) with ER agonist effects on bone and lipid metabolism and antagonistic effects on endometrium and breast tissue [1]. Building on our previous work [2], focused on ferrocenyl-benzo[b]thiophene derivatives as ER agonists, we have setup a library of metallocene-containing raloxifene analogues which were docked against ER α and β. The best ligands of the library are at least as

potent as raloxifene in binding to the receptor, albeit with a different pattern of interaction with the amino acid side chains. Results will also be discussed in terms of the contribution of each structural moiety of the group to the overall protein-ligand interaction. [1] Cohen, F.J., et al., *Obstet. Gynecol.* 95, 104 (2000). [2] Ferreira, A.P., et al., *Organometallics*, 28, 5412 (2009).

MEDI 263

2-Acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanyl-thiocarbonylamino)phenylthiocarbamoylsulfanyl]propionic acid – a novel glutaredoxin inhibitor

Satya S Sadhu¹, *satyasaisadhu@rediff.com*; Eduardo Callegari²; Xiangming Guan¹; Teresa M Seefeldt¹. (1) Department of Pharmaceutical Sciences, South Dakota State University, Brookings South Dakota 57005-0099, United States (2) BRIN-USDSM Proteomics Facility, University of South Dakota, Vermillion South Dakota 57069, United States

Protein S-glutathionylation is a process cells employ, when under oxidative stress, to protect the sulfhydryl group of proteins from irreversible oxidation through formation of a mixed disulfide bond. Glutaredoxin is the enzyme responsible for de-glutathionylation of proteins after resolution of the oxidative stress. Inhibition of glutaredoxin could be useful as a tool to study protein S-glutathionylation as well as other applications. For various reasons, no effective glutaredoxin inhibitor is currently available. 2-Acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylthiocarbonylamino)phenylthiocarbamoylsulfanyl]propionic acid (2-AAPA) was previously found to be a glutathione reductase inhibitor. Here we would like to report that the compound is also an effective irreversible glutaredoxin inhibitor. Mass spectrometric results along with substrate protection experiments confirmed the covalent modification at the active site. The K_i and k_{inact} of 2-AAPA against glutaredoxin were determined to be 91.3 μM and 0.13 min^{-1} , respectively. The ability of 2-AAPA to inhibit intracellular glutaredoxin was confirmed with a human ovarian cancer cell line.

MEDI 264

Novel 3H-spiro[naphtho[1,2-b][1,4]oxathiine-2,4'-piperidine]-5,6-diones as anticancer agents

David Vensel, *dvensel@arqule.com*; Manish Tandon; Syed M. Ali; Eugene Kelleher; Jason Hill; Hui Wu; Yanbin Liu; Patrick Hutchins; Rui-Yang Yang; Magdi Moussa; Jean-Marc Lapierre; Mark A. Ashwell; Woj Wrona. ArQule, Inc, 19 Presidential Way Woburn MA, United States

β -Lapachone (3,4-dihydro-2,2-dimethyl-2H-naphthol[1,2-b] pyran-5,6-dione), a natural product found in Pau d'arco trees (*Tabebuia impetiginosa*), has broad anti-cancer activities. ARQ 501, a fully synthetic version of β -lapachone, elevates E2F-1 levels

leading to the activation of the cell cycle checkpoint which results in the selective apoptotic cell death of cancer cells and is effective against human ovarian cancer and prostate cancer xenografts in mice. Promising anticancer activity has been observed in multiple Phase II studies. In this poster we describe the chemistry and structure-activity-relationships of series of 3H-spiro[naphtho[1,2-b][1,4]oxathiine-2,4'-piperidine]-5,6-diones from which a second-generation E2F-1 elevator was identified for clinical development. We present the strategy employed to develop the SAR within this series as well as the synthetic challenges encountered in the optimization.

MEDI 265

Small molecule Mer inhibitor for novel treatment of acute lymphoblastic leukemia

Chao Yang¹, *chaoyang@email.unc.edu*; Jing Liu¹; Weihe Zhang¹; Chatura Jayakody¹; Catherine Simpson¹; Victoria Korboukh¹; Jacqueline Norris-Drouin¹; Deborah DeRyckere²; William Janzen¹; Doug Doug Graham²; Xiaodong Wang¹; Stephen Frye¹. (1) Department of Pharmacy, University of North Carolina-Chapel Hill, Chapel Hill NC 27599, United States (2) Department of Pediatrics,, The University of Colorado, Denver, Aurora CO 80045, United States

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children. Current standards of treatment are significantly compromised by therapy-induced toxicity, development of resistance, and relapse. Ectopic expression of receptor tyrosine kinases Mer plays a critical role in the pathogenesis of ALL through initiation of anti-apoptotic signaling. Inhibition of Mer expression attenuates survival signaling and increases the efficacy of cytotoxic agents in xenograft mice model of leukemia. A series of novel pyrazolopyrimidine analogs shows good inhibition of Mer. Hit compound was identified and structure-activity relationship (SAR) has been established. Hit to lead optimization generates a series of lead compounds with sub-nanomolar *in vitro* potency versus Mer kinase and sub-micromolar cellular potency. Lead compounds were further evaluated for ADME, toxicity and selectivity against other kinase families with promising results. Among them, CY00076-78A1 was selected as a promising candidate. Further optimization toward a clinical candidate is underway.

MEDI 266

Development of clickable small molecule inhibitors of histone acetyltransferases

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Histone acetylation and deacetylation play essential roles in the regulation of gene transcription in eukaryotes. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) regulate these histone modifications. It is critical to develop small molecule modulators of these enzymes in order to study their functions and potential therapeutic applications. Genetic and other biological studies indicate that

dysfunction of HATs correlate with several human diseases including: cancer, neurodegeneration, asthma, diabetes, AIDS, cardiac hypertrophy, etc. Therefore, inhibitors of HATs might have therapeutic potential for treating these diseases. Despite the large number of potent and selective HDAC inhibitors, very few molecules are known to possess HAT inhibitory activity. Isothiazolones are a class of synthetic small molecule HAT inhibitors. We are developing a variety of synthetic isothiazolones including azide and alkyne functionalized derivatives for use as “clickable” probes of HAT activity in mammalian cell lines. We will present new synthetic routes to efficiently prepare benzo- and pyridoisothiazolones in a single reaction step from 2,2'-dithiobis-benzoic acid and 2,2'-dithiobis-3-pyridinecarboxylic acid. We will also present our studies on the HAT inhibitory potential of these small molecules and their utility as probes of HAT activity *in vivo*.

MEDI 267

Proteomimetics of coactivators of the androgen receptor

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Androgen receptor (AR) coactivator proteins play a significant role in the regulation of cell proliferation in prostate cancer by binding to AR and recruiting other coactivators that lead to gene transcription. We have designed a scaffold consisting of a bipolar 4, 4'-biphenyl core that mimics the alpha helical FXXLF motif of the coactivators, where L is leucine, F is phenylalanine, and X is any amino acid, and can successfully inhibit coactivator binding. A combinatorial approach was used in the synthesis of these molecules by constructing the amino and carboxy termini separately from 2-substituted phenols and coupling them together using Suzuki conditions. First and second generation libraries, as well as selected intermediates, have undergone time resolved fluorescence energy transfer, reporter gene and competitive binding studies on both the AR and the estrogen receptor alpha (ER α) and lead compounds have show low micromolar affinity.

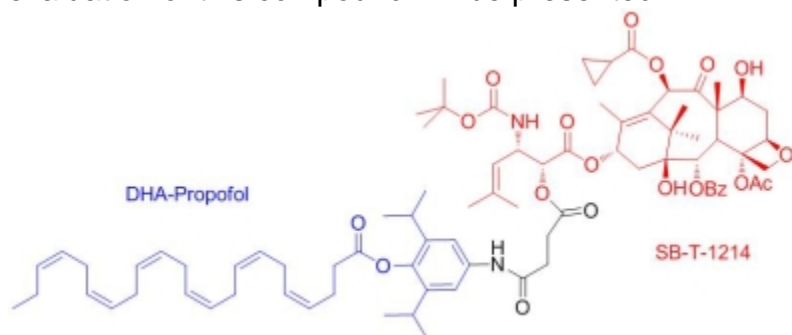
MEDI 268

Synthesis and biological evaluation of a novel drug conjugate bearing DHA-propofol and a second-generation taxoid

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Recently it has been shown that conjugation of docosahexaenoic acid (DHA) to the general anesthetic propofol results in a novel compound which selectively induces apoptosis in breast cancer cells. DHA also has been show to target cytotoxic agents to tumors resulting in tumor-specific accumulation *in vivo*, as exemplified by the DHA-

paclitaxel conjugate, Taxoprexin. To exploit these favorable properties, a novel conjugate linking a second generation taxoid, SB-T-1214, to DHA-propofol in the para position of the aromatic ring has been synthesized. The synthesis and biological evaluation of this compound will be presented.



MEDI 269

Synthesis and biological evaluation of the *R*- and *S*-enantiomers of the antitubulin 6-methyl cyclopenta[*d*]pyrimidines as cytotoxic agents that parallel predicted antitubulin activities

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Molecules that target microtubules in cancer cells are amongst the most utilized chemotherapeutic agents. However, problems such as multidrug resistance, poor water solubility, and/or toxicity are severe limitations for such agents. We recently reported a racemic mixture of a 6-CH₃ cyclopenta[*d*]pyrimidine that binds to the colchicine site on tubulin, exhibited potent antiproliferative activity and circumvented Pgp and β III tubulin mediated resistance. Molecular modeling studies predicted only a slight difference in the tubulin binding activities of the *R*- and *S*-enantiomers of *N*-(4-methoxyphenyl)-*N*,2,6-trimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-aminium chloride. The synthesis and evaluation of the individual enantiomers demonstrate a parallel between the predicted, docked activities and the observed activities of these enantiomers on tubulin and will be discussed.

MEDI 270

Synthesis and in silico and in vitro anticancer biological evaluation of *N*-aromatic sulfonylhydrazone derivatives

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Cancer is one of the most prevalent diseases in the world. Cancer cell resistance to chemotherapy is important to investigate new classes of agents for cancer treatment. In this work, initially we propose the synthesis of sulfo-lactams derivatives using classical Staudinger reaction as anti-cancer agents, but, results shows 3 series (propionic, phenoxy and phenyl acid) of *N*-aromatic sulfohidrazone derivatives with yields ranging from 2 to 44.6%. Additionally, the anti-tumor activity of obtained compounds was evaluated *in silico* and *in vitro* by the National Cancer Institute of United States. *In vitro* results showed that none of these compounds inhibit human tumor cell growth with values > 68%. Interestingly, antituberculosis and antiparasitic activities were showed in the *in silico* tests using the program PASS.

MEDI 271

Inhibition of anti-apoptotic Bcl-2 proteins by α -helix mimetics: A novel approach for cancer therapy

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One of the cardinal features of cancer is an evasion from programmed cell death (i.e., apoptosis) and it is manifested mainly by activation of anti-apoptotic members of Bcl-2 family proteins (e.g., Bcl-2, Bcl-xL and Mcl-1) and/or dysfunction of pro-apoptotic members (e.g., Bax, Bak, Bad, Bim, Bik and Puma). Hence, the Bcl-2 family has been considered as an attractive target to induce apoptotic cell death. Their structures consist of up to four conserved Bcl-2 homology (BH) domains that are found to be α -helical segments. In particular, an amphipathic α -helical BH3 segment of pro-apoptotic proteins (also known as minimal death domain) binds to a hydrophobic groove formed by BH1-3 domains of anti-apoptotic members and regulates the process of apoptosis by inducing oligomerization of Bax and Bak that in turn releases cytochrome c. Thus, we have developed helix-mimicking small molecules to emulate the BH3 domains of pro-apoptotic proteins as inhibitors of anti-apoptotic ones. A series of the BH3 mimetics were designed based on a rigid tris-benzamide scaffold that projects three side chain functionalities found at the i, i+4 and i+7 positions of the helical BH3 domains. The synthesized BH3 mimetics were evaluated on their inhibitory activities by various cell-based assays. A number of them showed strong inhibition of cell proliferation and induction of apoptosis as evidenced by caspase activation, DNA fragmentation, and PARP cleavage on various prostate cancer cell lines. All of these illustrate a high potential of the BH3 mimetics in disrupting Bcl-2 protein complexes.

MEDI 272

Spiruchostatin C, an HDAC inhibitory compound isolated from *Burkholderia thailandensis*

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Histone deacetylases (HDACs) are a family of enzymes involved in the regulation of eukaryotic and prokaryotic RNA synthesis, and have been validated as a target in the treatment of cancer. Continuing research in this area is aimed at finding inhibitors (HDACi's) having unique selectivity toward the 18 known HDACs, which could potentially be used to treat other types of cancer or as experimental tools in assessing the function of HDAC isoforms. In our lab, bioactivity guided fractionation of a *Burkholderia thailandensis* organic solvent extract has resulted in the isolation and identification of a new HDACi, a depsipeptide named spiruchostatin C. Structural elucidation was accomplished by LC/MS, advanced Marfey's analysis, and 1- and 2-D NMR techniques. In the NCI 60 human tumor cell screen, spiruchostatin C showed differential selectivity among cell lines compared to FK228, an HDACi approved for treatment of human cutaneous T-cell lymphomas.

MEDI 273

Anticancer activity of small molecule inhibitors of CREB-mediated gene transcription

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The cyclic-AMP response-element binding protein (CREB) is a stimulus-activated transcription factor. Its transcription activity entails its binding with CREB-binding protein (CBP) after CREB is phosphorylated at Ser133. A multitude of protein serine/threonine kinases including PKA, PKB and MAPK CREB can phosphorylate CREB. Since these pathways are often deregulated, CREB is found to be overactivated in variety of solid and liquid cancer tissues. These results suggest that chemical inhibitors of CREB-mediated gene transcription are promisingly novel cancer therapeutics. We previously identified naphthol AS-E as a small molecule inhibitor of CREB-CBP interaction with low micromolar potency. In this presentation, we will present data to show that this small molecule inhibitor exhibits antiproliferative activities in a variety of solid cancer cell lines through activation of apoptosis with low micromolar potency. Consistent with its mechanism of action, naphthol AS-E downregulates the expression of CREB target genes in cancer cells and its antiproliferative activity is dependent on CREB-CBP interaction in cells. Collectively, these studies represent the first small molecule inhibitor of CREB-CBP interaction with promising anticancer activities.

MEDI 274

Synthesis and biological evaluation of a novel DARPin-SB-T-1214 bioconjugate targeting CD-326 (EpCAM) overexpression on the cancer cell surface

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Traditional chemotherapy relies solely on the concept that rapidly dividing cancer cells will more readily uptake cytotoxic agents as compared with normal tissues. In actuality, many other types of rapidly dividing healthy tissues (e.g., bone marrow, hair follicles) can also be affected, leading to systemic toxicity. To address this issue, we have synthesized and evaluated several tumor-targeting drug conjugates bearing self-immolative disulfide linkers as well as vitamins and mAb's as tumor-targeting modules with substantial success. Building upon these successes, novel SB-T-1214 bioconjugate covalently linked, via a self-immolative disulfide linker, to a *Designed Ankyrin Repeat Protein* (DARPin, Ec4) was designed, synthesized, and evaluated *in-vitro* for both cytotoxicity and specificity. The synthesis of the novel tumor-targeting drug conjugate and results of their biological evaluation will be discussed.

MEDI 275

Design, development, and crystal structure of a cell permeable peptidomimetic inhibitor of mixed lineage leukemia 1 (MLL1)-WD repeat domain 5 (WDR5) interaction as a new approach in cancer therapy

Hacer Karatas^{1, 2, 3}, hkaratas@umich.edu; Elizabeth C. Townsend⁴; Yong Chen^{5, 6}; Deniz Bernard^{2, 3}; Yali Dou⁴; Ming Lei^{5, 6}; Shaomeng Wang^{1, 2, 3, 7}. (1) Department of Medicinal Chemistry, University of Michigan, United States (2) Department of Internal Medicine, University of Michigan, United States (3) Department of Comprehensive Cancer Care, University of Michigan, United States (4) Department of Pathology, University of Michigan, United States (5) Howard Hughes Medical Institute, University of Michigan, United States (6) Department of Biological Chemistry, University of Michigan, United States (7) Department of Pharmacology, University of Michigan, United States

MLL1 is a Histone-3 Lysine-4 (H3K4) methyl transferase, which is misregulated in leukemia. Upregulation of the target genes *HoxA9* and *Meis-1* links MLL1 with its tumorigenic properties. Therefore targeting the catalytic activity of MLL1 to repress expression of these genes could be a novel approach in cancer therapy. H3K4-methylation by MLL1 requires formation of a core complex consisting of MLL1, WDR5, RbBP5 and Ash2L, where the interaction of MLL1 with WDR5 is essential for catalytic activity. We developed a cell permeable peptidomimetic inhibitor of MLL1-WDR5 interaction, Compound-A (Mw=633Da), which binds to WDR5 with $K_d < 1$ nM, and can

efficiently inhibit catalytic activity of the reconstituted MLL1 core complex, *in vitro*. Furthermore Compound-A can block H3K4-trimethylation at *HoxA9* promoter and reduce *HoxA9* expression in MLL1-AF9 transformed BM cells. Crystal structure of Compound-A bound to WDR5 confirms our design strategy. These results suggest that inhibitors targeting MLL1-WDR5 interaction might have a therapeutic potential for cancer.

MEDI 276

Potential anticancer agents: Identification of small molecules as procaspase-3 activators

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Recent efforts for the treatment of cancer have focused on reestablishing the extrinsic or intrinsic apoptotic pathways, or both, by inhibiting antiapoptotic molecules, such as IAPs or c-FLIP, or by elevating levels of proapoptotic factors, such as Bcl-2 antagonists. Our primary goal for the treatment of cancer is the restoration of apoptosis in tumor cells via activation of procaspase-3. Procaspase-3 zymogen is the precursor of caspase-3, can be an important target of chemotherapy-induced tumor cell death. The concentration of procaspase-3 is elevated in a number of cancer cell lines, but there are no deleterious effects on the cancer cells unless it undergoes autocatalytic activation or proteolysis by caspase-9, that results in caspase-3 activation. Our preliminary data have shown that even the change in conformation of procaspase-3 results in its activation. Small molecules that selectively bind the dimer interface of procaspase-3 effectively kill cellular proteins without converting the proenzyme into caspase-3.

MEDI 277

Mitochondria targeted photodynamic therapy

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Photodynamic therapy(PDT) with a photosensitizer(PS) that targets mitochondria causes a prompt release of cytochrome c into the cytoplasm and activation of caspases that are responsible for cell degradation. Mitochondria have repeatedly been implicated as targets of porphyrin mediated PDT. A systematic study to direct the PDT drugs towards their cellular target, mitochondria of the cancer cell, is not fully explored. PDT causes mitochondrial damage and induces apoptosis. We hypothesize that construction of engineered targeted drug delivery systems to direct PDT drugs to the mitochondria would allow for effective phototherapeutics. This would result in a higher concentration

of singlet oxygen in the mitochondria of cancer cells. We have initiated the synthesis of a series of mitochondria targeting polymers to study nanoparticle(NP) assisted delivery and anticancer properties of metallophthalocyanines. One construct, which includes a mitochondria targeting moiety on NPs with encapsulated zinc-phthalocyanine(ZnPc) is represented in

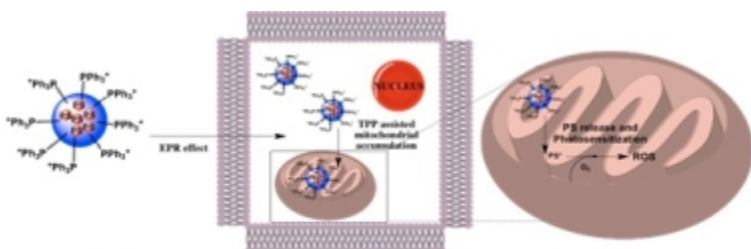


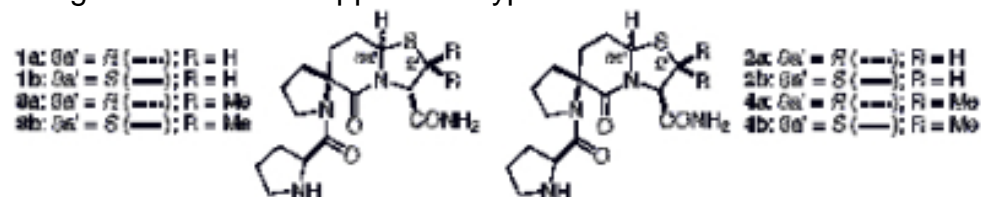
Figure 1: Mitochondria targeting delivery system and mitochondrial accumulation.

MEDI 278

Design of negative allosteric modulators of the dopamine D₂ receptor

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Prolyl-leucyl-glycinamide (PLG) is a unique endogenous peptide, which modulates dopamine receptor subtypes of the D₂ receptor family within the CNS in an allosteric manner. Previously, we demonstrated that diastereomeric pairs of 5.6.5-spirobicyclic lactam mimics of PLG differing in the stereochemistry at the C-8a' position (**1a/1b**; **2a/2b**) exhibited opposing modulatory activities at the D₂ dopamine receptor with **1a** and **2a** being positive modulators and **1b** and **2b** being negative modulators (Raghavan, B.; *et al. J. Med. Chem.* **2009**, 52, 2043). We hypothesized that the opposite bridgehead chirality resulted in a different pucker of the scaffold's thiazolidine ring, which in turn caused the C-2' methylene group to jut into a different area of topological space, thereby producing the negative modulatory effect. To test this hypothesis we designed the *gem*-dimethyl derivatives **3a**, **3b**, **4a**, and **4b** with the idea that such a substitution places steric bulk in the topological space that the C-2' methylene group occupies in the negative modulators. We postulated that with such a substitution we would be able to convert a positive modulator into a negative one. Pharmacological results on the designed molecules support our hypothesis.



MEDI 279

Structure-activity relationships of the systemically active peptide kappa opioid receptor antagonist zyklophin

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Kappa opioid receptor (KOR) antagonists have potential applications in the treatment of drug abuse and depression. We have prepared the peptide KOR selective antagonist zyklophin (Patkar, *et al.*, *J. Med. Chem.* **2005**, 48, 4500) that is systemically active and appears to cross the blood-brain barrier (Aldrich, *et al.*, *PNAS* **2009**, 106, 18396). Our objectives in the present study are to identify structural features of zyklophin that are responsible for its high KOR selectivity and antagonist activity, and to enhance its potency. We synthesized several zyklophin analogs with different N-terminal alkyl substituents, amino acid substitutions, and varying the residues involved in the cyclic constraint. The peptides were prepared by Fmoc (fluorenylmethyloxycarbonyl) solid phase synthesis with selective deprotection of the residues involved in the cyclization. Preliminary pharmacological data suggest that the fifth residue and the N-benzyl modification contribute to the peptide's KOR affinity and antagonist activity. Supported by NIDA grant R01 DA018832.



MEDI 280

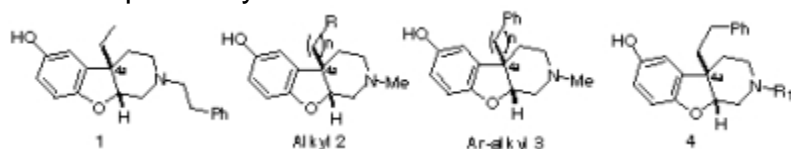
WITHDRAWN

MEDI 281

Probes for narcotic receptor mediated phenomena: Effect of C4a alkyl and ar-alkyl chain length on the opioid receptor affinity of N-methyl cis-4a-substituted 1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-c]pyridin-6-ols

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Benzofuro[2,3-*c*]pyridinols are partial structures of oxide-bridged phenylmorphans. Racemic *cis*-benzofuro[2,3-*c*]pyridin-6-ol with a phenethyl substituent on nitrogen and a C4a ethyl substituent **1** have been shown by Hutchison, et al. to have a high affinity for opioid receptors. As part of our continuing interest in benzofuro[2,3-*c*]pyridin-ol series of compounds, we have devised a simpler route for the synthesis of these compounds. This route enabled the studies on heretofore, unexplored analogs in the racemic *cis*-benzofuro[2,3-*c*]pyridin-6-ol series of compounds. A study involving the effect of chain length and substitution at the C4a position of *cis*-hexahydrobenzofuro[2,3-*c*]pyridin-6-ols was undertaken. The *N*-methyl-C4a-alkyl **2** and ar-alkyl **3** derivatives were synthesized and their affinity on opioid receptors was determined. Binding studies and functional assays revealed interesting trends. Data from this study will be discussed. Additional manipulations were made to modify the N-substitution. Synthesis and binding studies of the C4a phenethyl N-substituted derivatives **4** will also be presented.



MEDI 282

Design and synthesis of aminothiazole meriolin hybrid compounds as CDK5 inhibitors

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Cyclin dependent kinase 5 (CDK5) is a proline-directed serine/threonine kinase, which plays a prominent role in the pathology of Alzheimer's disease. CDK5 has been implicated in tau hyperphosphorylation that ultimately precipitates as neurofibrillary tangles (NFTs), a classic hallmark of Alzheimer's disease. The high homology between CDK5 with CDK2 (60% overall) has presented a challenge in developing selective inhibitors. Known compound **1** has been shown to have nanomolar inhibitory activity against CDK5. Novel hybrid analogs incorporating features of both **1** and Meriolin 5 (**2**) have been explored. The design, synthesis and enzymatic analysis of these new hybrid compounds will be presented.

MEDI 283

Discovery and structure-activity relationship studies of 1,3-cyclohexyl-diamides as novel mGlu5 receptor negative allosteric modulators

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Metabotropic glutamate receptors (mGluR) are a class of G-protein coupled receptors (GPCRs) that respond to the excitatory neurotransmitter glutamate. Eight mGluRs (mGluR1-8) have been identified and classified into three groups (group I, II, and III) based on their sequence homology, second messenger coupling, and pharmacology. Potential therapeutic applications for negative allosteric modulators of mGlu5 (mGlu5 NAM) include pain, acute migraine, anxiety, depression, fragile X syndrome, drug dependency, GERD, and Parkinson's disease. Herein we report a novel series of 1,3-cyclohexyl-diamides as mGlu5 NAMs. The structure-activity relationship and ADME properties of selective compounds of this chemotype will be presented.

MEDI 284

***N*-aryl pyrrolidinyl oxadiazoles as potent mGlu5 positive allosteric modulators**

Mathivanan Packiarajan¹, *matp@lundbeck.com*; Christine G. Mazza Ferreira¹; Sang-Phyo Hong¹; Andrew D. White¹; Gamini Chandrasena¹; Albert J. Robichaud¹; Robbin M. Brodbeck². (1) Chemical & Pharmacokinetic Sciences, Lundbeck Research USA, Paramus New Jersey 07652, United States (2) Synaptic Transmission, Disease Biology Unit, Lundbeck Research USA, Paramus New Jersey 0762, United States

Glutamate is the major excitatory neurotransmitter in the central nervous system acting on both ionotropic and metabotropic glutamate receptors. Eight subtypes of metabotropic glutamate receptors (mGluRs) have been identified and classified into group I (mGlu1 and mGlu5), group II (mGlu2 and mGlu3) and group III (mGlu4, mGlu6, mGlu7 and mGlu8) receptors. mGlu5 receptor modulation has been shown in various preclinical models to be potentially beneficial in a number of disease states. Activation of mGlu5 receptors has been postulated to ameliorate positive symptoms and cognitive deficits in schizophrenia. Through screening of our internal compound collection, we identified *N*-Aryl pyrrolidinyl oxadiazoles as leads which exhibit moderate EC₅₀ at the mGlu5 receptor. Optimization led to identification of highly potent compounds with acceptable *in vitro* metabolic clearance, CYP inhibition, hERG and PK properties. Here we report our efforts towards identification of *N*-Aryl pyrrolidinyl oxadiazoles as potent mGlu5 positive allosteric modulators.

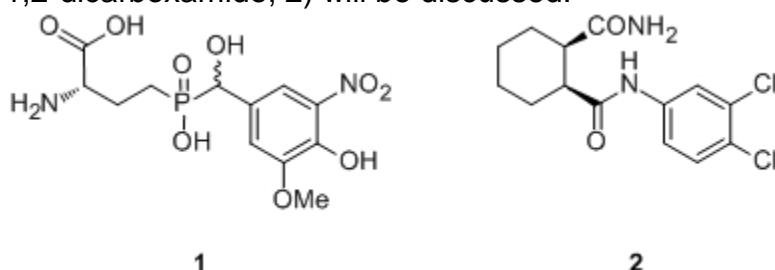
MEDI 285

Disposition characteristics and functional activity of LSP1-2111, an orthosteric Group III metabotropic glutamate receptor agonist

Dario Doller¹, *dado@lundbeck.com*; Sang-Phyo Hong¹; Kevin G. Liu¹; Maria D Bacolod¹; Michelle A Ubert²; Manuel Cajina¹; Francine Acher³; Paolo Gubellini⁴. (1) Chemical & Pharmacokinetic Sciences, Lundbeck Research USA, Paramus NJ 07652, United States (2) Synaptic Transmission Disease Biology Unit, Lundbeck Research

USA, Paramus NJ 07652, United States (3) Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologique, UMR 8601, CNRS, Université Paris Descartes, Paris Cedex, France (4) Institut de Biologie du Développement de Marseille - Luminy (IBDML), UMR 6216, CNRS/Aix-Marseille Université, Marseille, France

LSP1-2111 [(2S)-2-amino-4-(hydroxy(hydroxy(4-hydroxy-3-methoxy-5-nitrophenyl)methyl)phosphoryl)butanoic acid; **1**] is a novel orthosteric, preferential agonist of the mGlu4 receptor, a member of the group III mGlu receptor family. We report herein our studies on the *in vitro* pharmacology and CNS disposition of this compound. In addition, the *in vitro* brain electrophysiology studies showing the functional potentiation of the inhibitory actions of LSP1-2111 on EPSC by the mGlu4 positive allosteric modulator Lu AF21934 ((1S,2R)-N¹-(3,4-dichlorophenyl)-cyclohexane-1,2-dicarboxamide, **2**) will be discussed.



MEDI 286

WITHDRAWN

MEDI 287

Discovery and development of central nervous system (CNS) penetrant casein kinase 1 (CK1δ/ε) inhibitors

Jianke Li, jianke.li@pfizer.com; Jenifer A. Bradley; Michael A. Burge; Todd W. Butler; Ramalakshmi Y. Chandrasekaran; Angela C. Doran; Katherine E. Fisher; Paul Galatsis; David F. Gebhard; Ashley N. Hanks; Michele P. Kelly; John D. Knafels; Scot R. Mente; James D. Offord; Jeffrey F. Ohren; Vanessa Paradis; Blossom Sneed; Chakrapani Subramanyam; Todd A. Wisialowski; Laura E. Zawadzke; Travis T. Wager. Worldwide Research and Development, Pfizer, Groton CT 06340, United States

CK1 delta (CK1δ) and CK1 epsilon (CK1ε) are closely related members of a family of seven mammalian serine/threonine protein kinases previously known as casein kinases that have been identified as key regulatory factors in the control of circadian rhythms. Therefore, inhibitors of CK1δ/ε may be of therapeutic value in circadian rhythm disrupted disorders such as: jet lag, shift work and psychiatric disorders (i.e. treatment resistant depression and bipolar). In this work, we'll disclose the structure activity relationships (SAR) and kinase selectivity for a set of novel CK1 inhibitors. Further, the application of structure based drug design that transformed a p38 single point hinge binder into a selective CNS penetrant two point binding CK1 inhibitor will be described.

MEDI 288

Synthesis and evaluation of thiazolo[4,5-d]-pyrimidines as corticotropin releasing factor receptor antagonists

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Corticotropin releasing factor(CRF) is a 41 amino acid endogenous neuropeptide synthesized by specific hypothalamic nuclei in the brain and involved in the regulation of the Hypothalamus-Pituitary-Adrenal (HPA) axis. It is the principle modulator of mammalian physiological and behavioral responses to stress. Physiological responses of CRF are mediated through two receptors namely CRF1 and CRF2. CRF1 mediates normal responses to stress and CRF2 appears to play an important role in fine-tuning stress responses. Thus CRF represents new opportunity for the treatment of major depression and anxiety. Various peptide and non-peptide molecules are shown to inhibit CRF and thiazolo [4,5-d]-pyrimidines are one of them. We have prepared various derivatives of the fused thiazolo-pyrimidines as non-peptide CRF receptor antagonists. Few of the derivatives were analyzed for their effect on cell viability, effect on CRF1, Serotonin, CREB1, Dopamine transporter, MAO-A, NPY and Dopamine β -hydroxylase gene expression in α T3-1 pituitary mouse cell lines and Cyclic AMP levels. The gene expression studies were compared with known antagonist Antalarmin. A Few of the derivatives were shown to have comparable effects with Antalarmin in up- regulating gene expression and reducing Cyclic AMP levels. The binding affinities for these compounds using the CRF receptors will be measured to select lead compounds that can be further evaluated for their potential antianxiety and antidepressant properties.

MEDI 289

Tetra-alkyl bis-phosphates as bivalent inhibitors of butyrylcholinesterase: Compounds with potential for the treatment of Alzheimer's disease

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Butyrylcholinesterase (BChE) is a non-specific cholinesterase found in blood plasma with unknown physiological function. It is thought to play a role in growth and development and to act as a scavenger of cholinergic toxins as well as having an auxiliary role in synaptic transmission. BChE, like AChE, can hydrolyze acetylcholine.

Since BChE activity in the brain of Alzheimer's patients is elevated 40-90% above normal, BChE inhibitors can increase acetylcholine concentration in the brain. Therefore, these inhibitors may hold promise in the treatment of cognitive loss due to Alzheimer's disease. Different structural variations of the bivalent inhibitors, tetra-alkyl bis-phosphates, were prepared and evaluated in vitro for their inhibitory activity against BChE to determine the optimal linker chain length between two phosphates and the alkyl groups in order to maximize inhibition. These bivalent inhibitors are thought to interact at two sites of the enzyme and, therefore, their inhibitory properties may be magnified.

MEDI 290

What it takes to make amphetamine act different than dopamine at the human dopamine transporter

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The predominant action of the human dopamine (DA) transporter (hDAT) is re-uptake of extracellular DA into presynaptic neurons; however exposure of hDAT to psychostimulants can result in a reverse effect. Amphetamine (AMPH) and AMPH-like compounds are hDAT substrates that increase extracellular DA by diminishing DA re-uptake and releasing DA stored in synaptic vesicles. Although DA and AMPH produce inward currents through hDAT, only S(+)AMPH induces a persistent inward current. This persistent depolarization of dopaminergic neurons may play a role in the behavioral effects of psychostimulants. To understand which structural features are important in recognition of DA-like vs AMPH-like substrates we synthesized AMPH/DA hybrids and recorded currents through hDAT expressed in *Xenopus laevis* oocytes. All compounds possessing hydroxyl group(s) on the benzene ring behaved like DA and did not produce a persistent depolarization. Based on these results lack of ring hydroxylation could be the key structural feature accounting for AMPH-like action at hDAT. [NIH RC1DA028112]

MEDI 291

Preparation of potential serotonin transporter (SERT) inhibitors for diagnosing depression

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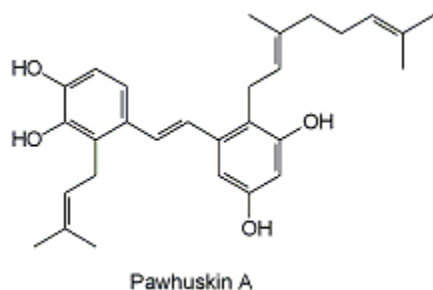
The relationship between serotonin and depression is well documented. Currently serotonin reuptake inhibitors (SSRIs) that target the serotonin transporter (SERT) are prescribed to treat millions of people with depression. Positron emission tomography (PET) imaging agents are useful for studying the binding sites of psychoactive drugs and monitoring the efficacy of such drugs. Several biphenylthiol imaging agents have been developed to study binding to SERT. On the contrary, ligands possessing a biphenyloxide core are relatively unexplored. Additionally, the routine use of several standard SERT tracers in medical centers is limited as many are labeled with carbon-11. Thus in this study, novel fluorine-containing biphenyloxides were prepared as potential probes to examine SERT binding in the brain.

MEDI 292

Synthesis of Pawhuskin analogs

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The isolation of the pawhuskins from the purple prairie clover *Dalea purpea* was reported in 2004. These compounds are prenylated stilbenes that bind to opioid receptors, an activity that is surprising given that they are non-nitrogenous. Pawhuskin A was shown to be a kappa selective antagonist with moderate binding affinity, and kappa antagonists are of special interest as potential treatments for stimulant abuse as well as other disorders. To help elucidate the novel pharmacophore of the pawhuskins, we have synthesized a number of new analogues. Our previous research on schweinfurthin synthesis employed a late-stage Horner–Wadsworth–Emmons condensation reaction to prepare the central stilbene olefin, and a similar chemical approach has been used to prepare pawhuskins. The chemical syntheses of these new pawhuskin analogues will be presented, along with hypotheses of opioid receptor interaction tested by further compound design.



MEDI 293

Conformationally rigid histone deacetylase inhibitors correct Δ F508-CFTR protein function

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Histone deacetylase (HDAC) inhibitors have shown partial efficacy toward correcting cystic fibrosis transmembrane conductance regulator (CFTR) protein function in $\Delta F508$ -CFTR models. While current treatment options for CF generally concentrate on disease symptoms such as management of inflammation and bacterial infection, therapy using HDAC inhibitors has the potential to treat and correct the underlying etiology associated with the disorder. Subsequently, we have synthesized conformationally well-defined cyclic tetrapeptide derivatives based on the natural product HDAC inhibitor Apicidin, in order to formulate a pharmacophore model to describe and enhance the bioactivity of these molecules. Through this study we have developed HDAC inhibitors which improve CFTR trafficking from the endoplasmic reticulum (ER) while ultimately increasing ion conductance across the plasma membrane of a lung epithelial cell line expressing $\Delta F508$ -CFTR.

MEDI 294

Design and synthesis of pyridazinone-phenethylamine based histamine H₃ receptor antagonists

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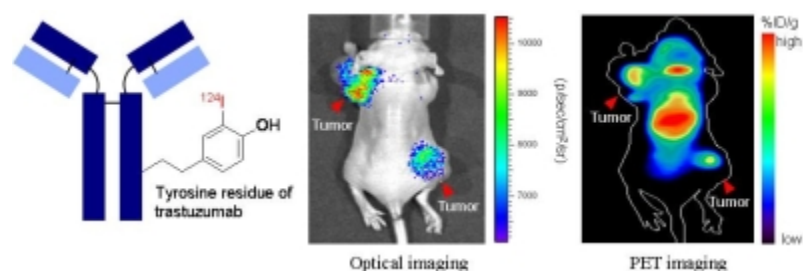
The histamine H₃ receptor (H₃R) is a G-protein coupled receptor (GPCR) located primarily in the brain that functions as an autoreceptor to modulate histamine release and as an inhibitory heteroreceptor, regulating the release of key neurotransmitters including acetylcholine (ACh), dopamine (DA), norepinephrine (NE), and serotonin (5-HT) that are involved in attention, vigilance, and cognition. Thus, H₃R antagonists may have utility in addressing a variety of CNS disorders associated with deficits in wakefulness, attention, and cognition, including attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), mild cognitive impairment, and schizophrenia. We have identified potent and orally bioavailable pyridazinone-phenethylamine analogs as histamine H₃ receptor antagonists. The synthesis, SAR, selectivity and pharmacokinetics of the pyridazinone-phenethylamine series will be presented.

MEDI 295

Facile preparation of optical/nuclear dual imaging probes using radionuclides

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Molecular imaging has become an indispensable research tool in many areas of biomedical science. Recently, even though it is still a challenge to integrate different imaging modalities into single imaging probes, multi-modality imaging has become possible due to the synthesis of hybrid dual- or triple-modality imaging probes. Here we report new facile methods for the preparation of optical/nuclear dual imaging probes using Cerenkov radiation. The characteristics of this technology as a new optical imaging modality were examined with respect to sensitivity, spatial resolution and tissue penetration. By simply radiolabeling antibodies with appropriate positron-emitting radionuclides, optical imaging-based dual modality imaging probes were easily prepared in high yields.



MEDI 296

Discovery of MK-3168: A clinical PET tracer as a target engagement biomarker for FAAH

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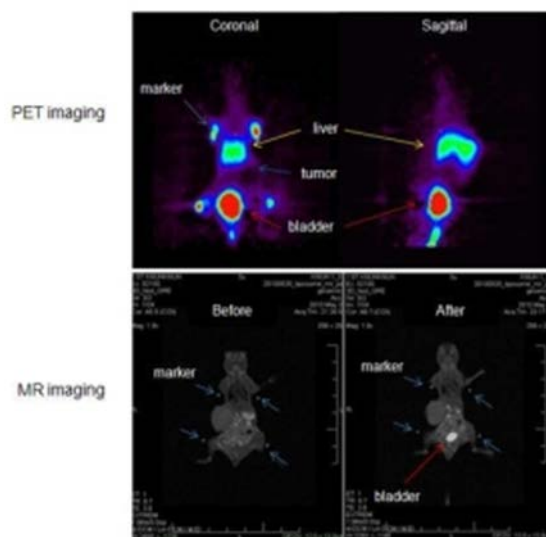
Fatty acid amide hydrolase (FAAH) is an integral membrane enzyme responsible for the breakdown of several fatty acid ethanolamide (FAE) signaling molecules, including the endocannabinoid arachidonoyl ethanolamide (anandamide, AEA), and the related lipids N-palmitoyl ethanolamide (PEA) and N-oleoyl ethanolamide (OEA). Inhibition of FAAH leads to elevated levels of these endogenous FAEs which act on cannabinoid, vanilloid, and other receptors to suppress pain transmission. Thus, a small molecule FAAH inhibitor is expected to provide therapeutic benefit in the management of inflammatory and neuropathic pain. Genetic and pharmacological data in rodents support a hypothesis that a high level of FAAH inhibition in the CNS is necessary for maximal analgesic efficacy. In order to provide data to guide dose selection for clinical studies and establish the relationship between enzyme inhibition and PD response, a clinical PET tracer suitable for measuring central occupancy of the FAAH enzyme is highly desirable. This presentation will discuss the FAAH program's target engagement strategies and focus on the efforts that led to the discovery of a novel FAAH PET tracer (MK-3168). Preclinical results in rhesus monkey and initial clinical results with this PET tracer will also be disclosed.

MEDI 297

Nuclear/MR dual-modality imaging agent based on liposome

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Liposome has been heavily utilized in drug delivery during last several decades, and now is seeking new application in imaging. Currently no single imaging modality provides all information for the characterization of complex body system. Instead, multimodality imaging, which combines two different imaging modality, gives various promising results. Especially the combination of nuclear imaging and magnetic resonance (MR) imaging will benefit due to their highly complimentary nature. Here we report new nuclear/MR dual-modality imaging probes based on liposome. Nuclear/MR dual imaging probe is prepared by incorporation of radio-iodine labeled lipophilic small molecule on liposome membrane and encapsulation of Gd complex inside of liposome. Gamma camera and MR imaging was successfully obtained in tumor-bearing mice using single dual imaging probes.



MEDI 298

WITHDRAWN

MEDI 299

New cephalosporin-derived inhibitor of β -lactamase: Synthesis, mechanism, and structure

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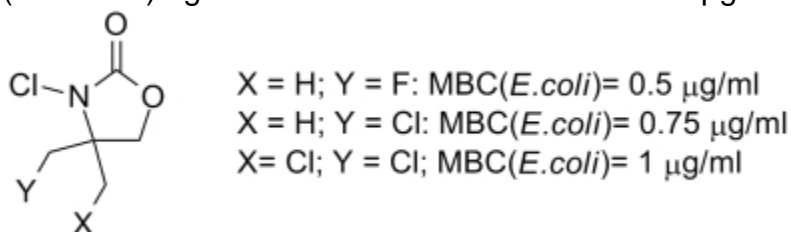
A new cephalosporin-derived inhibitor of class A β -lactamases was prepared and evaluated kinetically, spectroscopically, and crystallographically. This molecule inhibits via a novel mechanism that was confirmed crystallographically through a complex with the SHV-1 β -lactamase. The individual steps of the proposed mechanism were verified using Raman Spectroscopy.

MEDI 300

N-Chlorooxazolidin-2-ones as antimicrobial agents at neutral pH

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Previously synthesized *N*-chloramines have excellent activity at low pH; however, they can display reduced activity at physiological pH. Our recent structure activity/stability relationship efforts allowed us to identify new *N*-chlorooxazolidinones as agents with improved antimicrobial activity under a broad range of pH evaluations. Syntheses and *in vitro* antimicrobial activity of new 5-membered heterocycles are discussed, demonstrating potent antimicrobial compounds with bactericidal activity (1 hr MBC) against *Staphylococcus aureus* and *Escherichia coli* at 0.5 µg/mL and fungicidal activity (1 hr MFC) against *Candida albicans* as low as 8 µg/mL at pH 7.



MEDI 301

Methoxy β-Lactam derivatives as antimicrobial compounds

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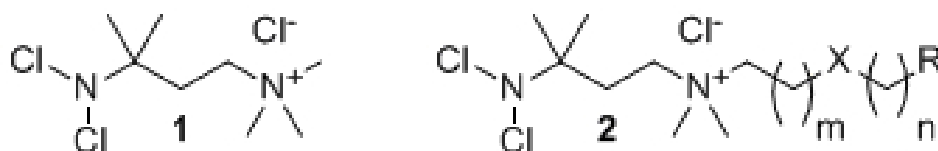
Adequate treatment of infectious diseases is under siege due to microorganisms that are resistant to currently available antibiotics. However, while drug-resistance exists in a wide range of clinically important microorganisms, new drug development has significantly lagged behind the need. To address that need, new approaches to drug development are necessary. Examples of such compounds prepared in our laboratories comprise of monocyclic beta-lactams with distinct substituent groups attached to an aromatic thiol, at the C4 of the β-lactam ring. These compounds, especially methoxy-thiophenols demonstrate activity specifically against *Mycobacterium tuberculosis* (Mtb). Structure-activity relationship (SAR) of these lactams against Mtb will be presented.

MEDI 302

Quaternary ammonium stabilized dichloroamines as antimicrobial agents

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N,N-Dichlorotaurine and *N*-chlorotaurine are potent, broad-spectrum antimicrobial agents produced by neutrophils during phagocytosis. Their use as a therapeutic agent is only limited due to their short shelf-life in solution at room temperature. Our structure activity/stability relationship study identified compound **1** as a water stable dichloroamine that retains excellent *in vitro* activity and good solution stability. A medicinal chemistry approach to improve the antimicrobial activity while maintaining aqueous stability of this class of agents will be examined. These analogs depict a profile of bactericidal activity (1 hr MBC) against *Staphylococcus aureus* and *Escherichia coli* in the range of 2-2048 µg/mL at both pH 4 and pH 7 with several analogs exhibiting potent activity. Furthermore, some analogs had fungicidal activity (1 hr MFC) against *Candida albicans* in the range of 4-2048 µg/mL at pH 7.



MEDI 303

Penicillin sulfones: An investigation of the effect of the 2'-substituent

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2'-Substituted penicillin sulfones (e.g. tazobactam) represent a clinically proven class of β -lactamase inhibitor. Still, little is known regarding the SAR of these compounds, particularly against the β -lactamases that have arisen in the past decade. We will report the synthesis and evaluation of a systematic series of 2'-substituted penicillin sulfones against a wide panel of serine β -lactamases, including class A and D carbapenemases.

MEDI 304

Synthesis and biological evaluation of new pyrimidin-2-one and 1,2,6-thiadiazines derivatives as anti-*Trypanosoma cruzi* agents

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Chagas' disease is caused by *Trypanosoma cruzi*, and is one the most important parasitic diseases in Latin America. Currently the only drugs available are Benznidazol and Nifurtimox, but they show toxicity and limited efficacy in the chronic phase. In order to address these deficiencies, our group synthesized two series of compounds derivatives of pyrimidin-2-one and 1,2,6-thiadiazines and then were tested *in vitro* on epimastigotes of *T. cruzi*. The most active compounds showed IC₅₀ values between 1.4 to 16 µM, and all of them had a nitro group in its structure. Finally, we test the inhibition capacity of those compounds on enzyme triosephosphate isomerase from *T. cruzi*, which is an enzyme involved in the glycolytic pathway of the parasite. Some of the test compounds showed IC₅₀ values of inhibition below 15 µM. Therefore, the results of this work have positive implications in the development of new agents anti-*T. cruzi*.

MEDI 305

Synthesis and biological evaluation of 2,7-di-ester quinoxaline 1,4 di-*N*-oxide as antituberculosis agents

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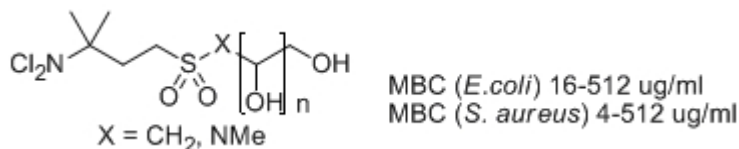
Tuberculosis is a high mortality disease worldwide and there are few therapeutic alternatives and an increasing drug resistance. Quinoxaline derivatives, which have shown diverse biological activities, interesting also have been reported with antituberculosis activity. In this study, we describe the synthesis a new series of compounds derivatives from 2,7-di-ester quinoxaline 1,4-di-*N*-oxide, which were obtained using the classical Beirut reaction with a yield of 5-30%. All the compounds have been characterized by means of Infrared and Nuclear Magnetic Resonance and tested *in vitro* on *Mycobacterium tuberculosis* H₃₇Rv. According to an analysis of structure-activity relationship we did determined that ethyl quinoxaline-7-carboxylate 1,4-di-*N*-oxide derivatives show a better inhibition activity on *Mycobacterium tuberculosis* H₃₇Rv than analogues of methyl quinoxaline-7-carboxylate, with a minimum inhibitory concentration values less than 6.25 µg/mL. These results show that ethyl quinoxaline-7-carboxylate 1,4-di-*N*-oxide could be considered as promising antituberculosis lead series.

MEDI 306

Sulfonyl-polyol *N,N*-dichloroamines with fast-acting, broad-spectrum antimicrobial activity

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Our ongoing efforts are discovering novel *N,N*-dichloroamines as potent antimicrobial and virucidal agents. These agents contain polyol side chains that impart unique physiochemical properties suitable for the treatment of infectious diseases of the skin and body surfaces. These agents show good activity against a broad range of bacterial and viral pathogens and a series of sulfonyl-polyols which show both bactericidal and virucidal activity will be discussed. For example, these compounds show 1-hour MBC of 16-512 ug/ml against *E. coli* and 4-512 ug/ml against *S. aureus*. The lead compounds were tested in a tissue culture irritancy model and showed only minimal irritation at the highest concentrations tested.



MEDI 307

Modifications on the side chain and the A-ring of diaryl ethers: Activity, kinetics, and drug-like properties

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The treatment of tuberculosis (TB) has become increasingly problematic due to the emergence of multi drug resistance. Diaryl ethers demonstrate potent antibacterial activity against drug resistant TB, by targeting the enoyl-acyl carrier protein reductase InhA. Previously, we reported modifications on the B-ring to improve the hydrophilicity and activity. We also identified slow-onset inhibitors of InhA, which is significant given previous correlation between slow-onset kinetics and the *in vivo* efficacy. Here, we present the optimization on drug-like properties of the diaryl ethers. Among 12 A-ring analogs and 11 side chain analogs, five compounds showed similar or improved inhibitory activity compared to parent compounds. With selective modulation on the shape of side chains, we disrupted the slow-onset kinetics with wtInhA and rebuilt it with InhA mutants. The results confirmed the key residues for slow-onset kinetics predicted by molecular dynamics simulation, which will inspire the further design of slow-onset InhA inhibitors.

MEDI 308

Effect of the aryl ring heteroatom attached at C4 on the antimicrobial activity of *N*-carbamylated β -Lactams

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New approaches to drug development are especially needed to target the organisms that are nearly universally resistant to antibiotics via production of enzymes that inactivate the drugs, e.g. β -lactamases. The design of antimicrobial compounds with new mode of action has reached a state of urgency. β -Lactams having arylthio-groups at C4, have been previously prepared in our laboratories and tested for intrinsic antimicrobial activity. From these azetidinone thioethers, the most active compounds are against two phylogenetically very distant bacterial species – *Moraxella catharralis* (*M. cat.*) and *Mycobacterium tuberculosis* (Mtb). The synthesis and structural-activity relationship of arylethers and arylselenylethers at C4 as compared to their arylthio counterparts is discussed.

MEDI 309

Enhancing in-vitro antimicrobial activity of some antibiotics with cyclopeptide

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A strategic approach to preventing antibiotic resistance is to treat bacterial infections with more than one drug at a time. Synergies of interaction can both increase the efficacy of the combination and reduce the probability of the bacterium's survival by developing a fortuitous mutation conveying resistance. Cationic cyclopeptides, in their capacity to compromise the integrity of bacterial membranes, could present itself as a valuable synergist for antimicrobial chemotherapy. In this study, we investigated the synergistic activities of some amphiphatic cationic cyclopeptides and five types of common antibiotics. Cyclopeptides containing a glutamyl residue were prepared by microwave-assisted solid phase peptide synthesis. Their invitro intrinsic antimicrobial activities were tested against Gram-positive and -negative bacteria by the microdilution antimicrobial susceptibility test. Synergistic activities were evaluated by conducting checkerboard titration assays. The correlation between antimicrobial and synergistic activities of the peptides with various types of antibiotics will be discussed.

MEDI 310

Development of PET radiotracers based on small molecule antitubercular drugs

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Via¹; Clifton E Barry¹. (1) National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville MD 20892, United States (2) National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, Rockville MD 20892, United States

The ability of drugs to penetrate tuberculosis (TB) lesions in the lung may be a predictor of efficacy of new TB treatments. Using ¹⁸F to radiolabel small molecule antitubercular drugs would allow Positron Emission Tomography (PET) imaging to analyze biodistribution of both novel and existing drugs in real-time to assess which compounds have the highest probability of becoming effective TB treatments. Additionally, PET imaging offers a non-invasive way to monitor disease state in patients or study animals. Response to chemotherapy can currently be monitored using [¹⁸F]-fluorodeoxyglucose (FDG); however, imaging agents that respond to bacterial load rather than secondary markers of infection such as inflammation would provide powerful tools to evaluate whether chemotherapy is effective. We have synthesized and evaluated both a [¹⁸F]-linezolid analog and a [¹⁸F]-PA-824 analog *in vivo* using rabbits infected with *Mycobacterium tuberculosis*. We are currently developing routes to other [¹⁸F]-labeled antitubercular drugs including fluoroquinolones.

MEDI 311

Towards the development of shelf-stable *N*-chloro amines as topical anti-microbial agents

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N-chloramine derivatives have long been known to be potent fast-acting antimicrobial agents. However, with the exception of chloramine-T, employed for prevention of gangrene in wounds during WW2, few *N*-chloramines have been commercialized as topical anti-microbial agents. NVC-422, a 2,2-dimethyl derivative of the unstable endogenous antimicrobial *N,N*-dichlorotaurine, exhibits good long-term aqueous solution stability, and was selected for evaluation in clinical trials for treatment of impetigo and viral conjunctivitis. Recent investigations on analogues of NVC-422 revealed that subtleties in the substitution pattern have significant influences on the stability of the parent *N*-chloro bond in aqueous solution, and ultimately on the shelf-life of the final therapeutic agent. We will explore the importance of the stereoelectronic environment around the nitrogen atom and the overall lipophilicity of the molecule as we sought to identify windows of stability during our continuing efforts to identify antimicrobial and virucidal agents with improved potency and spectrum.

MEDI 312

Development of an exploratory chemical probe for profiling histidine kinases

Samson Francis¹, *carlsone@indiana.edu*; **Kaelyn E Wilke**¹; **Erin E Carlson**^{1, 2}. (1) Department of Chemistry, Indiana University, Bloomington IN 47405, United States (2) Department of Molecular and Cellular Biochemistry, Indiana University, Bloomington IN 47405, United States

Two-component signal transduction systems (TCS) are commonly used by bacteria to couple environmental stimuli to adaptive responses through the use of gene regulatory systems. The high degree of homology around the ATP-binding sites of these systems suggests that appropriately designed compounds could serve as probes for the global profiling of histidine kinase activities. Using a focused-library virtual screen coupled with a receptor-based design strategy, we have identified a scaffold with potential utility for the exploration of the ATP-binding sites in TCS. The devised chemical probes will be utilized in the study of histidine kinase signaling in a diversity of organisms, with focus on *Streptococcus pneumoniae*.

MEDI 313

Towards the synthesis of novel boronates as potential HIV-1 protease inhibitors

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Drug discovery for HIV/AIDS has resulted in many life-saving therapies, making a profound impact on modern medicine. Current drug therapies exist, but are highly susceptible to resistance development, have poor bioavailability, and cause several side effects. For this reason, there is an urgent need to develop new types of inhibitors that address those difficulties. We are synthesizing novel boronates that were designed as dual-mode, competitive and associative, inhibitors of HIV-1 protease. Recent studies showed that boron-modified inhibitors have a higher affinity for the protease than their corresponding non-boronated analogs. Furthermore, the boron-modified structures were inhibitory to an HIV-1 protease variant that is resistant to several HIV-1 protease inhibitors. A library of both straight chain and cyclic boronates are being synthesized. The cyclic boronates, due to their structural rigidity, are expected to be better inhibitors than the straight chain compounds.

MEDI 314

Discovery and synthesis of cyclohexenyl derivatives as modulators of CC Chemokine Receptor 2 activity

Gregory D. Brown¹, *gregory.brown@bms.com*; **Douglas G. Batt**¹; **George V. Delucca**¹; **Qing Shi**¹; **Andrew J. Tebben**²; **Qihong Zhao**³; **Dauh-Rurng Wu**⁴; **Joel C. Barrish**¹; **Percy H. Carter**¹. (1) Department of Discovery Chemistry, Bristol-Myers Squibb Company, Princeton NJ 08543, United States (2) Department of Computer-Assisted Drug Design,

Bristol-Myers Squibb Company, Princeton NJ 08543, United States (3) Department of Discovery Biology, Bristol-Myers Squibb Company, Princeton NJ 08543, United States (4) Department of Discovery Chemical Synthesis, Bristol-Myers Squibb Company, Princeton NJ 08543, United States

CC Chemokine Receptor 2 (CCR2) is the primary chemokine receptor on monocytes recruited to sites of inflammation. On the basis of extensive pre-clinical studies, CCR2 inhibition is a mechanism of interest for the potential treatment of a number of diseases, including both atherosclerosis and diabetes. A novel cyclohexenyl series of CCR2 antagonists has been discovered. The cyclohexenyl exemplars are a series of small, rigid compounds exhibiting submicromolar binding affinity for CCR2. Modification of the substituents on the cyclohexene ring led to the identification of a group of potent CCR2 antagonists. The design, synthesis, and structure activity relationships of these cyclohexenyl derivatives will be reported.

MEDI 315

Identification and synthesis of potent and selective pyridyl-isoxazole based agonists of sphingosine-1-phosphate 1 (S1P₁)

Junqing Guo, junqing.guo@bms.com; Scott H. Watterson; James Kempson; Steve H. Spergel; Charles L. Langevine; Robert V. Moquin; Ding Ren Shen; Melissa Yarde; Mary Ellen Cvijic; Dana Banas; Richard Liu; Suzanne J. Suchard; Kathleen Gillooly; Tracy Taylor; Sandra RexRabe; Dave J. Shuster; Kim W. McIntyre; Georgia Cornelius; Celia Darienzo; Anthony Marino; Praveen Balimane; Luisa Saltercid; Murray McKinnon; Joel C. Barrish; Percy H. Carter; William J. Pitts; Jenny Xie; Alaric J. Dyckman. Bristol-Myers Squibb Research and Development, United States

Sphingosine-1-phosphate (S1P) is the endogenous ligand for the sphingosine-1-phosphate receptors (S1P₁₋₅). The interaction of S1P with the S1P receptors plays a fundamental physiological role in a number of processes including vascular stabilization, heart development, lymphocyte homing, and cancer angiogenesis. Agonism of S1P₁, in particular, has been shown to block lymphocyte trafficking from the thymus and secondary lymph nodes, resulting in immunosuppression. This presentation will outline the identification and synthesis of a potent and selective series of pyridyl-isoxazole based agonists of S1P₁. A compound in this series demonstrated efficacy when administered orally in a rodent model of arthritis.

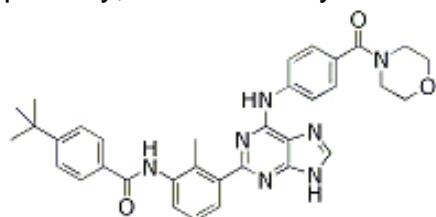
MEDI 316

Purine derivatives as potent BTK inhibitors for autoimmune diseases

Qing Shi, qing.shi@bms.com; Chunjian Liu; James Lin; Alaric J. Dyckman; Hedy Li; Lauren E. Vandevier; Cullen Cavallaro; Steven Spergel; James R. Burke; Andrew Tebben; Joann Strnad; Neha Surti; Jodi K. Muckelbauer; Kim McIntyre; Katerina

Leftheris; Percy H. Carter; Joseph Tino; George V. Delucca. Bristol-Myers Squibb, United States

Purine derivatives were investigated as potent and selective BTK inhibitors as exemplified by Compound 3. Structure activity relationship studies of the 2, 6, and 9 position substituents of the purine core and their importance to potency and selectivity will be highlighted. Further characterization of compound 3, including its X-ray structure determination in BTK, kinase selectivity profile, ADME properties, cellular functional potency, and its activity in animal models will also be discussed.



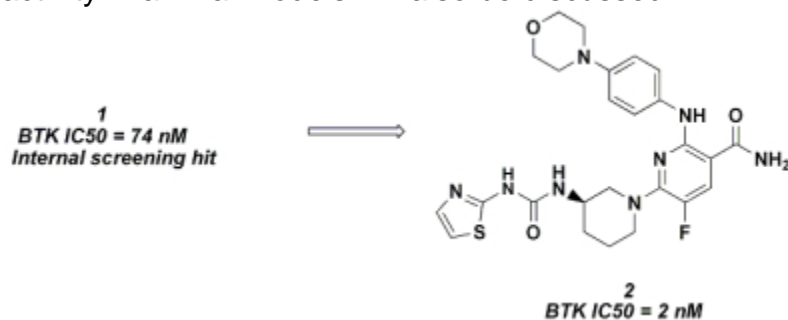
Compound 3

MEDI 317

Nicotinamide derivatives as potent BTK inhibitors for autoimmune diseases

George V De Lucca¹, george.delucca@bms.com; Qing Shi¹; Chunjian Liu¹; Andrew Tebben¹; Joann Strnad¹; Neha Surti¹; Jodi K Muckelbauer¹; Kim McIntyre¹; James R Burke¹; Katerina Leftheris¹; Percy H Carter¹; Joseph Tino¹; Chiehying Chang². (1) Research and Development, Bristol-Myers Squibb Company, Princeton New Jersey 08540, United States (2)

Starting from an internal screening hit (1) we were able to optimize this nicotinamide series to obtain potent and selective BTK inhibitors as exemplified by Compound 2. Structure activity relationship studies of the 2, 5, and 6 position substituents of the nicotinamide core and their importance to potency and selectivity will be highlighted. Further characterization of nicotinamides, including X-ray structure determination in BTK, kinase selectivity profile, ADME properties, cellular functional potency, and its activity in animal models will also be discussed.



MEDI 318

Synthesis and SAR of quinoxaline MK-2 inhibitors

Yonghan Hu¹, fred.hu@pfizer.com; Steve Kirincich¹; J. Christian Baber²; Satenig Guler³; Nikolaos Papaioannou¹; Kevin Parris¹; Steve Tam¹; Weiheng Wang¹; Julie Liu¹; Marina Shen¹; Lin-Ling Lin¹; Jean-Baptiste Telliez¹; Frank Lovering¹. (1) Pfizer Global Research and Development, Cambridge MA 02140, United States (2) Cubist, Lexington MA 02421, United States (3) Astra Zeneca, United States

MK2 is a Serine/Threonine kinase regulated by phosphorylation by p38 MAP kinase. MK2 knockout mice have been shown to be deficient in LPS-induced TNF production, a cytokine that plays a significant role in a number of inflammatory disease states including rheumatoid arthritis. MK2 knockout mice are also resistant to collagen induced arthritis. Compounds that inhibit MK2, therefore, could potentially be useful in the treatment of many TNF mediated diseases such as rheumatoid arthritis. In order to circumvent the metabolic liabilities of the lead benzothiadiazole **1**, we identified the isostere quinazoline **2** which proved to not form reactive metabolites. Structure based drug design resulted in compound **16** which has shown promising PK results and has fared well in the rat LPS-TNF model. Further improvements in drug-like properties and in the human whole blood potency will be necessary to further improve this series of MK-2 inhibitors.

MEDI 319

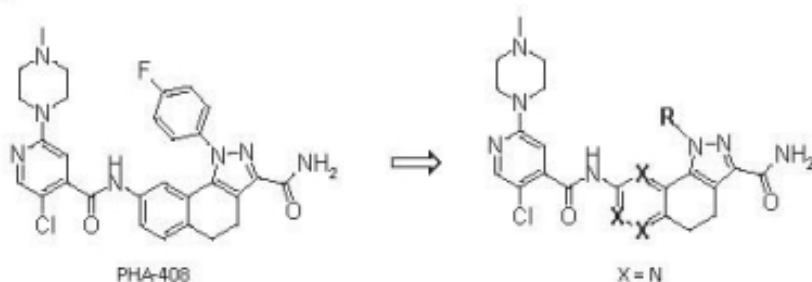
Strategic design and synthesis of analogs aimed at de-risking hERG and μ Ames liabilities of a potent and selective IKK-2 inhibitor

John R. Springer¹, john.r.springer@pfizer.com; Shaun R. Selness¹; Danny Garland¹; Richard F. Heier¹; Balekudru Devadas¹; Michele Promo¹; Serge G. Wolfson¹; Dominique Bonafoux¹; Yiding Hu²; Shentian Yang³; Sheri L. Bonar⁴; Sumathy Mathialagan⁴. (1) Department of Medicinal Chemistry, Pfizer Inc., Cambridge Massachusetts 02140, United States (2) Department of Pharmacokinetics and Drug Metabolism, Pfizer Inc., Chesterfield Missouri 63017, United States (3) Department of Structural Chemistry, Pfizer Inc., Chesterfield Missouri 63017, United States (4) Department of Inflammation Biology, Pfizer Inc., Chesterfield Missouri 63017, United States

A previously described series of Aminopyridinecarboxamide-based inhibitors of IKK-2 were synthesized and tested against human recombinant IKK-2 and IL-1 β stimulated synovial fibroblasts and PHA-408 (Fig. 2) was identified as a potent, selective, and efficacious ATP-competitive inhibitor of IKK-2 yet this class of inhibitor produced signals in both hERG and μ Ames toxicity assays. Our efforts focused on developing a strategic design approach to de-risk hERG and μ Ames liabilities of this chemical class providing

a path forward for treatment of inflammatory diseases.

Fig. 2



MEDI 320

Discovery of indazoles as inhibitors of Tpl2 kinase

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Tpl2 kinase is a serine/threonine kinase in the MAP3K family. Tpl2 activates the MEK/ERK signaling pathway and stimulates TNF production. Tpl2 is important for both TNF production and signaling. Therefore, Tpl2 has become a highly desirable target for treating Rheumatoid Arthritis. The synthesis and structure-activity studies of a novel series of indazoles as inhibitors of Tpl2 kinase are described.

MEDI 321

Structure – activity relationships of pyrrole based S-nitrosogluthione reductase inhibitors

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The enzyme S-nitrosogluthione reductase (GSNOR) is a member of the alcohol dehydrogenase family (ADH) that regulates the levels of S-nitrosothiols (SNOs) through catabolism of S-nitrosogluthione (GSNO). GSNO and SNOs are implicated in the pathogenesis of many diseases including those in respiratory, cardiovascular, and gastrointestinal systems. The pyrrole based **N6022** was recently identified as a potent, selective, reversible and efficacious GSNOR inhibitor which is currently in clinical development for acute asthma. We describe here the synthesis and structure activity relationships (SAR) of novel pyrrole based analogues of **N6022** focusing on imidazole

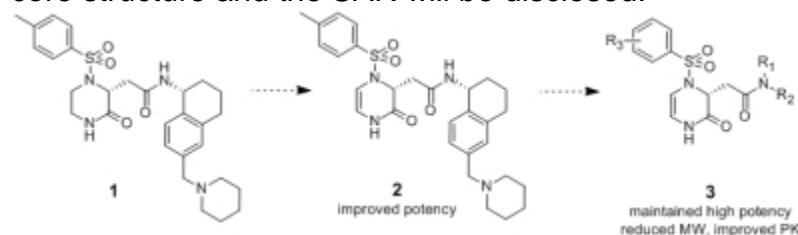
replacement, scaffold modification and propionic acid modifications. We have identified a number of potent and novel GSNOR inhibitors that demonstrate efficacy in an OVA-induced asthma model in mice.

MEDI 322

Discovery of dehydro-oxopiperazine acetamides as novel Bradykinin B1 receptor antagonists for treatment of pain and inflammation

Wenyuan Qian Qian, *wqian@amgen.com*; Jian Jeffrey Chen; Jason Human; Toshi Aya; Jiawang Joe Zhu; Tanya Peterkin; Kaustav Biswas; Leyla Arik; Eileen Johnson; Gondi Kumar; Smriti Joseph; Janan Jona. Department of Chemistry Research & Discovery, Amgen, Thousand Oaks CA 91320, United States

Kinins are released at sites of tissue injury and produce pain and inflammation via activation of constitutively expressed Bradykinin B2 and inducible Bradykinin B1 receptors. In the last decade there has been intense interest in identifying orally active Bradykinin B1 receptor antagonists for the treatment of inflammation and pain. We recently discovered oxopiperazine acetamide **1** as a potent B1 antagonist. In this presentation, we will report a new dehydro-oxopiperazine acetamide series **2** that results in higher binding potency. This improvement in potency, compared to its saturated counterpart, enabled further modifications leading to compounds **3** which can maintain potency while significantly lowering the overall molecular weight compared to **2**. As a result of the reduced molecular weight, some of these truncated analogs exhibit improved PK properties. The synthesis of the chiral dedydro-oxopiperazine acetamide core structure and the SAR will be disclosed.



MEDI 323

Inhibition of COX-2 and ASIC-3 by structural analogs of diclofenac

Tyler Rose¹, *trose@usn.edu*; **Daniel Williams**¹, *dwilliams@student.usn.edu*; Kyle Hansen¹; Ronald Bodi McEwen¹; Emmanuel Deva²; Eric Lingueglia². (1) Roseman University of Health Sciences, South Jordan Utah 84095, United States (2) Institut de Pharmacologie Moléculaire et Cellulaire, Valbonne, France

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) whose actions are thought to be at least partially mediated by its inhibition of cyclooxygenase (COX) isozymes (COX-2 IC₅₀ = 50 nM). Unlike most other NSAIDs, diclofenac also modestly inhibits (IC₅₀ = 92 μM) acid-sensing ion channel 3 (ASIC-3), a sodium-conducting ion channel

activated by low pH that is likely to be involved in pain signaling. In light of disadvantages associated with NSAIDs (gastrointestinal and cardiovascular side effects and an analgesic ceiling) and opioid drugs (addiction, physical dependency), compounds that target ASIC-3 may provide an attractive new approach to pain pharmacotherapy. Our goal is to modify the structure of diclofenac in an attempt to minimize COX inhibition and maximize ASIC-3 inhibition. To this end, we will describe the synthesis of a series of diclofenac analogues and the results of their use in inhibition assays against COX-2 and ASIC-3.

MEDI 324

Design and synthesis of novel pyrrolo[1,2-*b*]pyridazine derivatives of phosphodiesterase 4 (PDE4) inhibitors

Mitsuaki Okumura¹, *mitsuaki.okumura@jp.astellas.com*; Yoshito Abe¹; Tsuyoshi Mizutani¹; Kouzo Sawada²; Kazuhiko Ohne¹; Noriaki Maeda³; Takashi Manabe²; Makoto Inoue¹. (1) Drug Discovery Research, Astellas Pharma Inc., Tsukuba Ibaraki 305-8585, Japan (2) QA, RA and Pharmacovigilance, Astellas Pharma Inc., Itabashi-ku Tokyo 174-8612, Japan (3) Drug Discovery Research, Astellas Pharma Inc., Chuo-ku Tokyo 103-8411, Japan

PDE4 is an enzyme responsible for the hydrolysis of cyclic 3',5'-adenosine monophosphate (cAMP). PDE4 inhibitors are believed to be beneficial for the treatment of various inflammatory disease, because elevation of cAMP is known to suppress activation of inflammatory cells. Pyrrolo[1,2-*b*]pyridazine series of PDE4 inhibitors were discovered and optimization of the series led to the identification of ASP9831, a potent inhibitor with excellent oral bioavailability. ASP9831 significantly reduced the elevation of alanine aminotransferase (ALT) at 1.0 mg/kg in a rat model of D-galactosamine-induced acute hepatitis without delaying gastric emptying.

MEDI 325

NS-78, novel vitamin D₃ antedrug as new agent for psoriasis

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Plaque psoriasis, a common form of psoriasis, is a chronic, hyperproliferative, inflammatory disease of skin, characterized by red, scaly, raised plaques. Topical products of vitamin D₃ analogs have become first-line therapy for plaque psoriasis. The mode of action is thought to be an inhibition of epidermal cell proliferation, an induction of epidermal cell differentiation, an inhibition of IL-1/6/8 production in epidermal cell, an inhibition of T cell activation, and so on owing to vitamin D₃ receptor activation. Vitamin D₃ analogs currently used for psoriasis include calcipotriol, tacalcitol, maxacalcitol (only available in Japan) and calcitriol. Although topical products of vitamin D₃ are currently

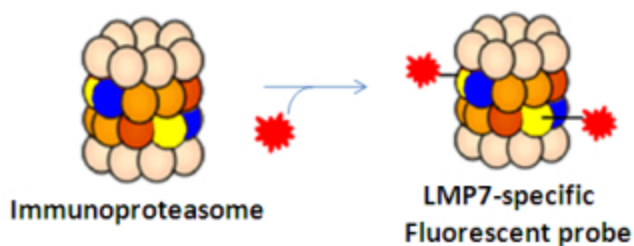
first-line therapy for plaque psoriasis, drug compliance of the products is rather low since those vitamin D₃ analogs have to be administered twice-daily. Furthermore, a dosing of the products is limited because of high risk of hypercalcemia due to their intrinsic hypercalcemic action and/or severe local irritation in skin. Antedrug is defined as an active synthetic derivative that is designed to undergo biotransformation to an inactive form upon entry in systemic circulation. Based on the concept of antedrug, we have been developing NS-78, a novel vitamin D₃ analog, in order to overcome problems of existing topical products of vitamin D₃ analogs. The features of NS-78 are; (1) Higher pharmacological activity than currently available topical vitamin D₃ products, (2) Fast metabolization in systemic circulation, (3) Local activity in skin maintained for 24 hours (It is expected to be effective by once-daily administration), and (4) Lower risk of hypercalcemia and milder local irritation in skin than calcipotriol. Based on the above characteristics, NS-78 is expected to be an effective treatment for psoriasis, which overcomes the problems of existing topical vitamin D₃ products.

MEDI 326

Development of activity-based fluorescent probes targeting the immunoproteasome

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The proteasome plays an important role in regulating intercellular protein homeostasis by initiating degradation of intercellular proteins conjugated with polyubiquitin chains. The immunoproteasome, an alternative proteasome form, is constitutively expressed in cells of hematopoietic origin and can also be induced in normal cells by exposure to cytokines. Exposure to these stimuli induces the synthesis and incorporation of immunoproteasome catalytic subunits LMP2, MECL1 and LMP7, replacing their constitutive proteasome counterparts Y, Z and X respectively. The major function of the immunoproteasome is thought to promote adaptive immune responses. Recent studies have associated elevated levels of the immunoproteasome catalytic subunits with some pathological disorders such as cancer and autoimmune disorders. However, the detailed understanding of immunoproteasome function is still lacking, due in large part to the lack of appropriate molecular probes selectively targeting immunoproteasome. This talk will focus on the synthesis and characterization of active site-directed molecular probes that selectively inhibit LMP7, a major catalytic subunit of the immunoproteasome. Also, the development of fluorescent imaging probes targeting LMP7, which allow rapid detection and localization of catalytically active immunoproteasome, will be discussed. These imaging probes provide a valuable tool to analyze the functions and dynamics of the immunoproteasome in living cells.



MEDI 327

CCR2b-specific antagonists part 4: New design, synthesis, and SAR of (4-heteroarylthiophen-2-yl)methyl-(R)-3-aminopyrrolidine derivatives

Tomohide Ida, *t.ida@teijin.co.jp*. Teijin Pharma Limited, Japan

The Chemokine Receptor CCR2b is a member of G protein coupled receptor family and has been known to play an important role in chronic inflammatory diseases including multiple sclerosis, rheumatoid arthritis and atherosclerosis. In our exploring studies for the CCR2b receptor antagonists we constructed a QSAR model of the ligand binding site with several compounds by using Sybyl/CoMFA and the other method, and we have made use of the model in the optimization of 1-substituted-(R)-3-aminopyrrolidines. After the synthetic work of various derivatives, we have identified (4-heteroarylthiophen-2-yl)-methyl-(R)-3-aminopyrrolidine derivatives with potent inhibitory activity. We will present the structure-activity-relationship of the (R)-3-aminopyrrolidine series with early ADME properties and so on.

MEDI 328

Discovery and SAR of novel heteroarylphenyl aniline derivatives as Rho kinase inhibitors

Junko Watanabe¹, *junko.watanabe@jp.astellas.com*; **Takeshi Terasawa**²; **Kouzo Sawada**³; **Yoshimasa Imamura**¹; **Hiroki Fukudome**¹; **Jun Maeda**¹; **Nobuaki Takeshita**¹; **Makoto Takeuchi**¹; **Mitsuaki Ohta**¹. (1) Drug Discovery Research, Astellas Pharma Inc., Japan (2) Astellas Research Technologies Co. Ltd., Japan (3) QA, RA and Pharmacovigilance, Astellas Pharma Inc., Japan

Rho kinase (ROCK), a 160-kDa serine/threonine kinase, is the effector of Rho, a small GTP-bound protein. Two isoforms, ROCK1 and ROCK2, have been identified, and these enzymes are involved in a variety of physiological functions including cytoskeletal control, cell growth, cell migration, apoptosis and many aspects of inflammatory responses. Therefore ROCK inhibitor has the potential to be a medicine for inflammatory diseases; rheumatoid arthritis and osteoarthritis etc. We selected Wf-536, a known ROCK inhibitor, as a lead compound. Modification of this compound produced

novel heteroarylphenyl aniline derivatives as potent and selective ROCK inhibitors. We also discovered that several compounds induced an analgesic effect on a monoiodoacetate-induced arthritis model in rats with ED₅₀ values of less than 1 mg/kg after oral administration. We will report the synthesis, the SAR and the pharmacological properties of the heteroarylphenyl aniline derivatives.

MEDI 329

Oxazolecarboxamide derivatives as novel IRAK-4 inhibitors

Hiroshi Inami¹, *hiroshi.inami@jp.astellas.com*; Tsuyoshi Mizutani¹; Junko Watanabe¹; Hiroyuki Usuda¹; Shinya Nagashima¹; Tomonori Ito¹; Naohiro Aoyama¹; Toru Kontani¹; Hisashi Hayashida²; Takeshi Terasawa²; Ayako Moritomo¹; Takeshi Ishikawa¹; Kazumi Hayashi¹; Makoto Takeuchi¹; Mitsuaki Ohta¹. (1) Drug Discovery Research, Astellas Pharma Inc, Japan (2) Astellas Research Technologies Co. Ltd, Japan

Interleukin-1 receptor associated kinase-4 (IRAK-4) is an essential molecule in Toll-like receptors (TLR)- and IL-1 receptor-mediated signaling pathways and thought to be an attractive therapeutic target for various autoimmune and inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus (SLE), diabetic nephropathy, gout and sepsis. In our search for novel IRAK-4 inhibitors, high-throughput screening of our compound library and subsequent structural modifications resulted in the discovery of a novel series of oxazolecarboxamide derivatives showing potent inhibitory activity with nanomolar IC₅₀ values. Moreover, selected compounds exhibited significant effects in rodent arthritis models as well as kidney disease models after oral administrations. Synthesis, structure–activity relationships and pharmacological properties of the oxazolecarboxamide derivatives will be presented.

MEDI 330

KMO inhibitors as potential therapeutic agents for the treatment of HD: Towards proof-of-concept studies

Christopher Yarnold¹, *chris.yarnold@evotec.com*; Michael Prime¹; Dirk Winkler²; Maria Beconi³; Fred Brookfield¹; Chris Brown¹; Stephen Courtney¹; Andreas Ebner²; Rachel Grigg¹; Estelle Hamelin-Flegg¹; Peter Johnson¹; Volker Mack²; Richard Marston¹; William Mitchell¹; Paula Pena¹; Laura Reed¹; Selvaratnam Suganthan¹; Ignacio Munoz-Sanjuan³; Eric Schaeffer³; Leticia Toledo-Sherman³; Derek Weddell¹; Naomi Went¹; Christin Winkler²; John Wityak³; Celia Dominguez³. (1) Evotec (UK) Ltd, Abingdon Oxon OX14 4SA, United Kingdom (2) Evotec AG, Hamburg, Germany (3) CHDI Foundation, Los Angeles California CA 90045, United States

Kynurenine mono-oxygenase (KMO) is an enzyme in the Kynurenine Pathway (KP) that catalyses the conversion of kynurenine (KYN) into 3-hydroxykynurenine (3-HK), a precursor of quinolinic acid (QA), a neurotoxin. It has been shown that in early stage Huntington's Disease (HD) brains, 3-HK is increased in both striatum and cortex.

Furthermore, QA and 3-HK levels were found to be elevated in the striatum, cortex and cerebellum of R6/2 HD transgenic mice. Through extensive medicinal chemistry it has become apparent that the KMO inhibitory activity of our lead molecule is highly dependent on the presence of an acidic moiety in the molecule. Compounds with acidic moieties do not penetrate the brain well and this poster describes our efforts to investigate the Structure Activity Relationship of these inhibitors and our strategy for modifying this moiety to achieve brain penetration. We present progress towards the identification of compounds for proof-of-concept studies in HD.

MEDI 331

Development of potent and selective transglutaminase-2 inhibitors for the treatment of Huntington's disease

Michael E Prime¹, michael.prime@evotec.com; John Wityak²; Stephen Courtney¹; Christopher Yarnold¹; Fred Brookfield¹; Richard Marston¹; Peter Johnson¹; Osamu Ichihara¹; Sabine Schaertl³; Andreas Ebner³; Andreas Scheel³; Ignacio Munoz-Sanjuan²; Celia Dominguez²; Douglas Macdonald²; Leticia Toledo-Sherman²; Maria Becon². (1) Discovery Chemistry, Evotec, Abingdon Oxfordshire OX14 5NB, United Kingdom (2) CHDI, Los Angeles California 90045, United States (3) Corporate Headquarters, Evotec Hamburg, Hamburg, Germany

Tissue transglutaminase 2 (TG2; TGM2; human Gene ID# 7052) is a multi-functional protein primarily known for its calcium-dependent enzymatic activity of crosslinking proteins via an isopeptide bond formation between glutamine and lysine residues. TG2 over-expression and activity has been found to be associated with Huntington's disease (HD) by several investigators. Interestingly, genetic deletion of TG2 in two different transgenic HD mouse models, results in improved phenotypes including a reduction in neuronal death and prolonged survival. Here we report a novel class of TG 2 inhibitors which have been developed from a small non-selective molecule to analogues that display nanomolar potencies with desired selectivity profiles over the other TGase isoforms. We also report the identification of a significant plasma stability issue following in vitro DMPK profiling and the subsequent development of a second-generation inhibitor with improved stability and potential for proof-of-concept in vivo studies.

MEDI 332

Tetrahydrofuro[3,4-b]pyridiones as prolyl hydroxylase inhibitors

Vincent J Colandrea¹, vince_colandrea@merck.com; Joshua G McCoy¹; Kothandaraman Shankaran¹; Deodial Guadeen¹; Kenneth Alves²; Julie DeMartino³; Richard Hajdu²; Carol Ann Keohane²; Russell Lingham³; Fredric Masse²; Scott Salowe³; Sharon Tong⁴; Junying Wang⁴; Matthew Wyvratt¹; Jeffrey J Hale¹. (1) Rahway Discovery Chemistry, Merck Research Laboratories, Rahway NJ 07065, United States (2) Rahway Central Pharmacology, Merck Research Laboratories, Rahway NJ 07065, United States (3) Department of Immunology, Merck Research Laboratories, Rahway NJ

07065, United States (4) Rahway Preclinical DMPK, Merck Research Laboratories, Rahway NJ 07065, United States

Hypoxia-inducible factor (HIF) is a α/β heterodimeric gene transcription factor for a multitude of genes including glycolytic enzymes, erythropoietin and VEGF. Levels of HIF are regulated metabolically via hydroxylation of proline residues on the α -subunit by a family of hydroxylases known as prolyl hydroxylases (PHD's). Inhibitors of the three isoforms of PHD's (PHD1-3) stabilize HIF and consequently stimulate the production of red blood cells (RBC's) through the modulation of erythropoietin (EPO), the EPO receptor, and proteins responsible for iron handling and transport. As a result, much interest has arisen in small molecule PHD inhibitors for the treatment of anemia. Herein, we will discuss our lead optimization efforts on the tetrahydrofuro[3,4-b]pyridone scaffold.

MEDI 333

Isolating bioactive compounds from medicinal plants of Puerto Rico

XueQiang Zha, zhaxueqiang@yahoo.com.cn; **Vibha Bansal**, vibha.bansal@upr.edu; Aixa Castro; Ricardo Diaz; Yadhira Lugo Jose. Department of Chemistry, University of Puerto Rico at Cayey, Cayey Puerto Rico 00736, Puerto Rico

Urokinase type Plasminogen Activator (uPA) has been implicated as a key mediator of cellular invasion and metastasis of tumor cells, angiogenesis and chronic wounds. Inhibitors of uPA are thus good candidates for use as drugs in treatment of cancer and other disease situations where uPA-driven degradation of extra cellular matrix or uPA-dependent cell migration is thought to be important. Plants of 15 different species were collected from Puerto Rico. The collected samples were dried to a constant weight in an oven at 40-50°C and then ground to fine powder. The dried powders were extracted with methanol and partitioned with petroleum ether (PE), chloroform (CHL), ethyl acetate (EA) and n-butanol (BUT) in a serial manner. The extracts were dried and re-dissolved in methanol and tested for the presence of inhibitors of uPA using Fibrin Plate Assay. Among the 15 plants, the inhibition of uPA was observed in 8 species.

MEDI 334

SiliaBond HOBt: A versatile and reusable silica-supported reagent used in API

Raif Kadri, raifkadri@silicycle.com; David Dubé; Olivier Marion; Geneviève Gingras; François Béland. SiliCycle Inc., Quebec City Quebec G1P 4S6, Canada

It has been reported in the literature that 25% of all synthetic pharmaceutical drugs contain an amide function¹. 1-hydroxybenzotriazole (HOBt) is commonly used as an amide coupling precursor in peptides synthesis which is a great interest for API preparation. Moreover, utilization of HOBt can increase yield and decrease racemization occurring during the amide synthesis. By bonding HOBt on silica, the possibility of

explosion caused by the exothermic decomposition of dry HOBt is eliminated. The newest addition to the **SiliaBond Reagent** product line, **SiliaBond HOBt**, can be easily activated in the same condition as in homogeneous solution by using preferably a base such as N,N-diisopropylethylamine. Furthermore, this supported reagent can be recycled many times without limitation in the performance. This poster presents the usefulness of the **SiliaBond HOBt** for the amine protection using benzylcarbamate and the synthesis of N-hydrosuccinimide ester using anhydrides or activated carboxylic acids.

MEDI 335

Hit to lead approaches: Working in enabled chemical space to achieve rapid project progression

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The pharmaceutical industry is coming under increasing pressure to identify quality chemical matter with reduced costs and shorter time frames. In our Hit to Lead chemistry group, we have been able to efficiently convert early lead structures into high quality lead matter that has enabled rapid project progression and testing of biological mechanisms. In a number of projects we used iterative library design and synthesis to achieve these objectives. This presentation will highlight strategies and approaches our team has used to quickly move projects through key decision points.

MEDI 336

GALAS modeling methodology applications in the prediction of the drug metabolism related properties

Pranas Japertas¹, pranas.japertas@acd labs.com; Remigijus Didziapetris¹; Justas Dapkunas^{1,2}; Andrius Sazonovas¹. (1) ACD/Labs, Inc., Vilnius LT-08117, Lithuania (2) Department of Biochemistry and Biophysics, Vilnius University, Vilnius LT-08117, Lithuania

This work investigates the possibilities of effective third-party model utilization in predicting drug metabolism related properties. A major problem is that training sets rarely cover chemical space and experimental protocols of 'in-house' projects. A method is needed that allows any company to tailor a third-party predictive algorithm to its needs using proprietary data. We present GALAS modeling methodology that provides a possibility to expand the Applicability Domain of the models with the help of a custom database of experimental values. Use of the method is illustrated with examples of its

application in predicting cytochrome P450 substrate and inhibitor specificity as well as regioselectivity. Relatively small amount (3 to 5) of similar compounds has to be added to substantially improve predictions for compounds not represented in the original training set. Similarly the models are shown to be able to utilize experimental data obtained using different protocol compared to training set data.

MEDI 337

Analysis of screening results from a proprietary inactive kinase-focused screening library

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Department of Chemistry, ArQule, Inc., Woburn MA 01801, United States

Recently we described how an understanding of the role of hydrophobic residues within the ATP-binding cleft of inactive protein kinases can be utilized for the identification of selective, small molecule kinase inhibitors. Utilizing this knowledge we employed an *in silico* approach for the creation of a proprietary, focused library having a bias toward the inactive conformation of protein kinases with excellent Rule of 5 compliance. A key feature of the construction of this library has been the use of parallel chemistry to provide rapid compound selection. This library has been screened against a wide variety of kinases and herein we provide an analysis of the screening results using three Ligand Efficiency Indices: PEI, BEI, SEI. These indices provide an effective framework for the interpretation of screening data. Applications of this methodology in the selection and optimization of lead compounds from hit generation programs for multiple kinases will be presented.

MEDI 338

Improving kinase inhibitor selectivity through exploring adjacent non-conserved pockets

Kristoffer R Brandvold, *kristofb@umich.edu*; Matthew B Soellner. Department of Medicinal Chemistry, University of Michigan, Ann Arbor MI, United States

The study of protein kinase activity has implications in the understanding of both healthy and disease-state biological systems. Selective regulation of kinase activity using small molecules is challenging due to the inherent promiscuity of conventional ATP-competitive inhibitors. The authors will present a strategy designed to improve upon the selectivity of ATP-competitive inhibitors by incorporating elements that interact with variable regions outside of the canonical ATP-pocket. The approach employs an ATP-competitive inhibitor adorned with an alkyne, which allows for facile conjugation with a variety functionalized azides through click chemistry. Biochemical and cellular applications will be discussed.

MEDI 339

Deuterium in drugs for cardiovascular disease: Design and synthesis of deuterated cilostazol and ranolazine analogs with enhanced metabolic stability

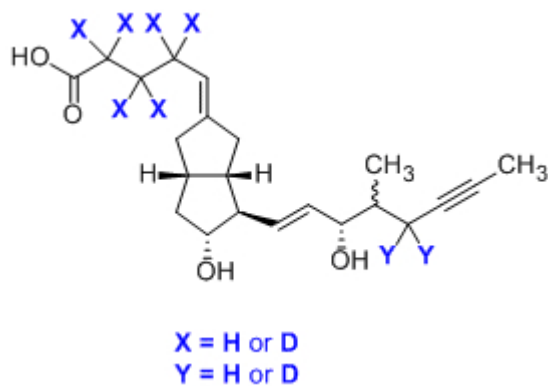
Julie F Liu, jliu@concertpharma.com; Vinita Uttamsingh; Sophia Nguyen; Gary W Bridson; Adam J Morgan; Craig E Masse; Roger Tung; Scott Harbeson; Richard Gallegos. CoNCERT Pharmaceuticals, Inc., Lexington MA 02421, United States

Cilostazol (Pletal®) and ranolazine (Ranexa®) are approved in the US and abroad as cardiovascular agents. Cilostazol, indicated for the reduction of symptoms of intermittent claudication, is a PDE3 inhibitor which affects platelet aggregation and vasodilation. Ranolazine, a treatment for chronic angina, provides anti-ischemic and anti-anginal effects through an undetermined mechanism. Both drugs are dosed orally BID and are extensively metabolized, primarily by CYP3A. We have prepared novel deuterium-modified analogs of cilostazol and ranolazine in which certain hydrogen atoms have been selectively replaced with deuterium. Deuterium effects on metabolism are unpredictable, even when deuterium is inserted at a known site of metabolic oxidation. Our research has identified multiple novel deuterated analogs of cilostazol and ranolazine with enhanced metabolic stability. Syntheses of these compounds via routes which allow for precise deuterium incorporation will be described. Data comparing our precision-deuterated analogs to cilostazol and ranolazine with respect to metabolic clearance will be presented.

MEDI 340

Design and synthesis of deuterated iloprost analogs with potential for enhanced pharmacokinetic properties

Bhaumik A Pandya, bpandya@concertpharma.com; George Borg; Craig E Masse; Scott Harbeson; Roger Tung. Medicinal Chemistry, Concert Pharmaceuticals Inc., Lexington MA 02421, United States



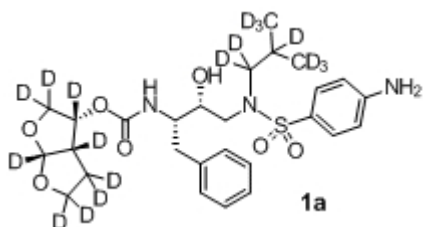
As part of our ongoing effort to apply the Deuterated Chemical Entity Platform (DCE Platform™) to clinically validated drugs, the synthesis of deuterated analogs of the PGI₂ mimetic iloprost (Ventavis®) was carried out. The DCE Platform™ has been shown to positively impact certain drugs' absorption, distribution, metabolism and/or excretion

(ADME) properties creating the potential for improved drug efficacy, safety, and tolerability. Deuterated isotopologs of iloprost, an approved agent for pulmonary arterial hypertension (PAH), have the potential to provide an improved pharmacokinetic profile relative to iloprost, which has a human half-life of 25-30 minutes. The design and synthesis of deuterated analogs employing routes amenable to precise deuterium incorporation will be presented.

MEDI 341

Design and synthesis of deuterated darunavir analogs with enhanced pharmacokinetic properties

Adam J Morgan, amorgan@concertpharma.com; Craig E Masse; Sophia Nguyen; Changfu Cheng; Gary Bridson; Vinita Uttamsingh; Roger Tung; Scott Harbeson. Department of Medicinal Chemistry, Concert Pharmaceuticals, Inc., Lexington MA 02421, United States



As part of an ongoing effort to apply the Deuterated Chemical Entity Platform (DCE Platform™) to clinically validated drugs, the synthesis of deuterated analogs of the HIV protease inhibitor darunavir (Prezista®) was carried out. The devised synthetic routes allowed for site selective deuterium incorporation with high levels of isotopic purity. Several deuterated analogs displaying marked levels of *in vitro* metabolic stabilization were identified with compound **1a** exhibiting a 39% increase in *in vitro* half life. Details of the convergent synthetic routes to the isotopologs along with results from human liver microsomal assays will be presented.

MEDI 342

Strategies in lead optimization: Shedding light on the relationship between lipophilicity and clearance

Dario Doller, dado@lundbeck.com. Chemical & Pharmacokinetic Sciences, Lundbeck Research USA, Paramus NJ 07652, United States

Projecting human pharmacokinetics is a key step in de-risking drug candidates prior to entering the clinic. Low clearance compounds present advantages, and significant efforts are devoted to engineer this property into biologically active chemotypes. There is some perception that lowering *cLogP* is a sound medicinal chemistry strategy to produce drug candidates with low *in vivo* clearance. Experimentally, hepatic

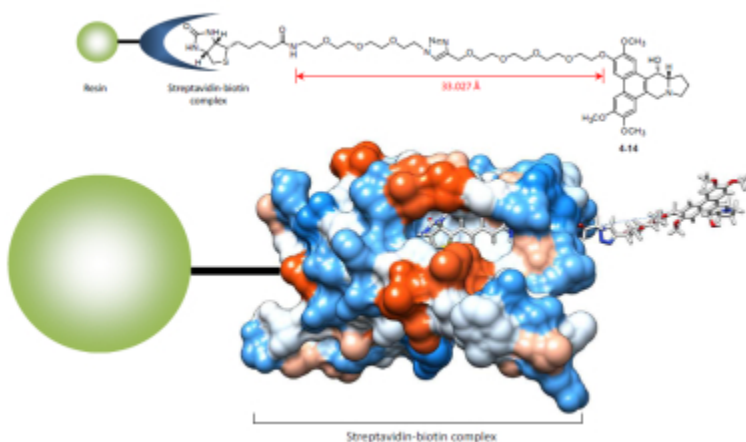
metabolism liabilities are estimated using *in vitro* intrinsic clearance (CL_{int}) determinations with pooled human microsomes, and applying the well-stirred model to produce a projected hepatic clearance, CL_H . While ignored early on, the free fraction in the microsomal incubation ($f_{u_{mic}}$) is now recognized as a key parameter in the well stirred equation. Extensive research has led to a number of simple mathematical relationships linking $f_{u_{mic}}$ and $cLogP$. We present simulations of intrinsic unbound clearance ($CL_{int,u}$) suggesting that the apparent linear relationship with $cLogP$ is driven mainly by the dependence of $f_{u_{mic}}$ on $cLogP$.

MEDI 343

Synthesis of a biotin conjugate of the tylophorine analog DCB-3503 bearing a novel PEG-based tether

Samson Francis, dcbaker@utk.edu; David C. Baker. Department of Chemistry, University of Tennessee, Knoxville TN 37996-1600, United States

In our continued efforts towards probing the physiologically relevant protein binding partners of the phenanthrolizidine alkaloids, we wish to report the design and synthesis of a biotinylated derivative of the tylophorine analog DCB-3503 bearing a novel tether. The interaction between a molecular probe and its target is typically governed by variables such as linker length and composition; as such, we chose to incorporate a PEG-based linker of exceptional length, between the active head unit and the biotin moiety. Attachment of a heterobifunctional PEG derivative to the phenanthrene skeleton of DCB-3503 followed by “click” conjugation with PEG-functionalized biotin facilitated access to the target probe. Modeling studies indicated that a significant portion (21.365 Å) of the DCB-3503-biotin conjugate remained sufficiently exposed even after simulated streptavidin capture, making it suitable for targeting any potentially elusive binding partners. Furthermore, owing to its exceptional length and enhanced hydrophilicity, this novel tether may find uses in other applications such as drug delivery.

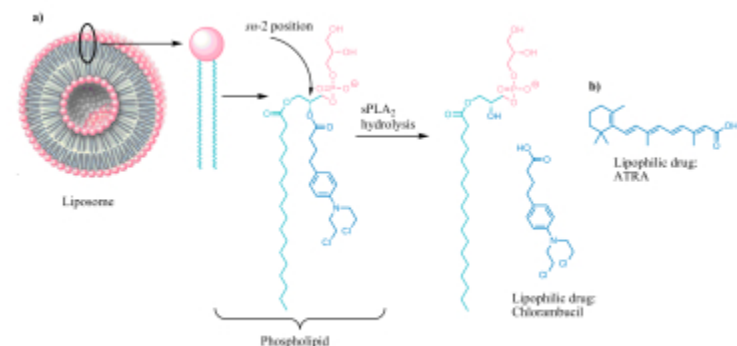


MEDI 344

Synthesis and structure-activity relationship of liposomal substrates for phospholipase A₂

Hélène Viart, hmvi@kemi.dtu.dk; Mads H. Clausen. Department of Chemistry, Technical University of Denmark, Kgs. Lyngby 2800, Denmark

A recent innovation in the use of liposomes as drug delivery systems consists of covalently attaching an anticancer drug at the *sn*-2 position of phospholipids. However, some of those lipids could not be hydrolyzed by sPLA₂.



Phospholipid prodrugs as drug delivery systems: a) Chlorambucil and b) ATRA have been linked to the *sn*-2 position of the phospholipids but the ATRA substrate could not be hydrolyzed.

Steric bulk in the vicinity of the *sn*-2 position appears to prevent hydrolysis of the substrate. Structurally different lipids have been synthesized and formulated as liposomes, subjected to sPLA₂ and the hydrolysis rates have been compared to Molecular Dynamics simulations of the enzyme/substrate complexes.

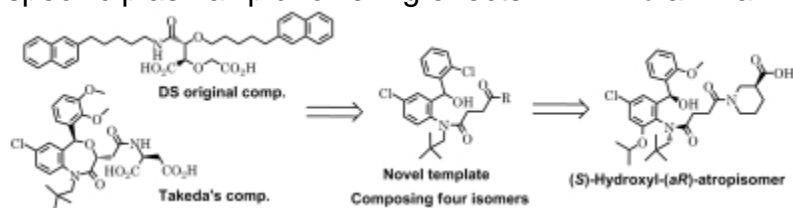
MEDI 345

Discovery of atrop fixed alkoxy-aminobenzhydrol derivatives: Novel, highly potent and orally efficacious squalene synthase inhibitors

Masanori Ichikawa¹, ichikawa.masanori.uf@daiichisankyo.co.jp; Aki Yokomizo²; Masao Itoh²; Noriyasu Haginoya²; Kazuyuki Sugita³; Hiroyuki Usui²; Koji Terayama⁴; Akira Kanda⁵. (1) Lead Discovery and Optimization Research Laboratories I, Daiichi Sankyo Co., LTD., 1-2-58, Hiromachi, Shinagawa-ku Tokyo 140-8710, Japan (2) Lead Discovery and Optimization Research Laboratories II, Daiichi Sankyo Co., Ltd. Tokyo, Japan (3) Institute of Molecular and Cellular Biosciences Tokyo, Japan (4) Cardiovascular-Metabolics Research Laboratories, Daiichi Sankyo Co., Ltd. Tokyo, Japan (5) Biological Research Laboratories, Daiichi Sankyo Co., Ltd. Tokyo, Japan

To obtain efficient small molecule squalene synthase inhibitors, we designed and prepared a flexible 2-aminobenzhydrol template. The X-ray co-crystallographic study revealed our compound's unique 11-membered ring conformation binding mode with an intramolecular hydrogen bond. However, the template was composed of a pair of easy rotatable atropisomers. In an effort to fix the isomerization, we found a highly potent alkoxy-aminobenzhydrol scaffold. Moreover, two of the series of compounds exhibited

specific plasma lipid-lowering effects in *in vivo* animal models.

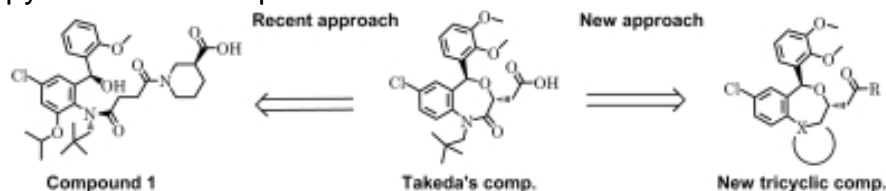


MEDI 346

Discovery of novel tricyclic compounds as squalene synthase inhibitors

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In the present article, we have reported the design, synthesis, and identification of highly potent benzhydrol derivatives as squalene synthase inhibitors (compound 1). However, there was concern regarding the possibility of the isomerization of benzhydrol part via carbo cation in acidic condition. In order to obtain a more stable and efficient inhibitor in the body environment, we focused on Takeda's benzoxazepin ring and designed a new tricyclic scaffold by the incorporation of heterocycles. Prepared pyrrolobenzoxazepine derivatives showed *in vitro* and *in vivo* effective activities.

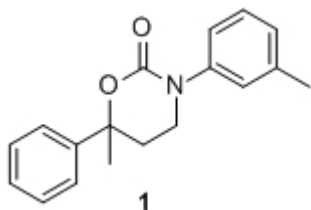


MEDI 347

Structure-based design and optimization of 1,3-oxazin-2-one inhibitors of 11 β -hydroxysteroid dehydrogenase type 1

Colin M Tice, ctice@vitaerx.com; Zhenrong Xu; Wei Zhao; Salvacion Cacatian; Yuan-Jie Ye; Suresh B Singh; Peter Lindblom; Brian M McKeever; Paula M Krosky; Barbara A Kruk; Jennifer Berbaum; Richard K Harrison; Judith A Johnson; Yuri Bukhtiyarov; Reshma Panemangalore; Boyd B Scott; Yi Zhao; Joseph G Bruno; Jennifer Togias; Joan Guo; Rong Guo; Gerard M McGeehan; Linghang Zhuang; Wei He; David A Claremon. Vitae Pharmaceuticals, Fort Washington PA 19034, United States

11 β -HSD1 is an attractive target for the treatment of diabetes. Application of a proprietary structure-based drug design methodology led to the rapid identification of oxazinone **1** with an IC₅₀ value of 42 nM. Optimization around this scaffold afforded a lead compound with an IC₅₀ value of 0.75 nM. This compound was orally bioavailable and, in cynomolgus monkeys, reduced plasma cortisol levels following a cortisone challenge.



MEDI 348

Indolyl/dihydroindolyl N-glycinamides as potent NPY5 antagonists

Lingyun Wu¹, lwu@lundbeck.com; **Kai Lu**¹; **Mathivanan Packiarajan**¹; **Vrej Jubian**¹; **Gamini Chandrasena**¹; **Toni Wolinsky**²; **Mary W Walker**². (1) Chemical & Pharmacokinetic Sciences, Lundbeck Research USA, Paramus NJ 07652, United States (2) Neuroinflammation Disease Biology Unit, Lundbeck Research USA, Paramus NJ 07652, United States

Neuropeptide Y (NPY) is a 36 amino acid neuropeptide widely expressed in the central and peripheral nervous systems possessing a diverse array of biological functions including influencing blood pressure, food intake, circadian rhythms, and stress sensitivity. NPY exerts its effects through interaction with specific receptors of the GPCR super family. Five NPY receptors have been identified to date (Y1, Y2, Y4, Y5, and Y6). Subtype specific ligands are needed to evaluate the therapeutic potential of modulating the brain's neuropeptide Y system. Through our efforts to investigate the utility of modulating the NPY system, a benzothiazepine glycinamide was identified as an NPY5 antagonist lead. Optimization efforts targeting improvements in potency, microsomal stability, and PK properties culminating in the discovery of a new class of structurally novel indolyl/dihydroindolyl glycinamides as NPY5 antagonists will be presented.

MEDI 349

Synthesis and biological evaluation of dual PPAR/cannabinoid ligands

Ruth Pérez-Fernández¹, rperezf@iqm.csic.es; **Nieves Fresno**¹; **Manuel Macías**²; **José Elguero**¹; **Juan Decara**²; **Fernando Rodríguez de Fonseca**²; **Pilar Goya**¹. (1) Instituto de Química Médica, CSIC, Madrid 28006, Spain (2) Fundación Hospital Carlos Haya, Spain

Peroxisome proliferator-activated receptors (PPARs) belong to the superfamily of nuclear receptors and consist of three isoforms. They are involved in the regulation of glucose and lipid metabolism, as well as in adipogenesis, feeding and other processes such as inflammation and neuroprotection. Therefore, they are interesting targets in medicinal chemistry. It has been reported that combining cannabinoids with other compounds (other cannabinoids or PPAR agonists) increases their therapeutic potential. We report the synthesis and evaluation of dual ligands targeting the cannabinoid receptor and PPARs. They are the first examples of dual compounds with nanomolar affinity for both receptors. Therefore, it can be considered an interesting lead in the search of a new class of dual ligands capable of modulating metabolism with potential neuroprotective activities.

MEDI 350

Design, synthesis and SAR of triazolopyridazine based cannabinoid-1 receptor antagonists

Yanting Huang¹, yanting.huang@bms.com; Chongqing Sun¹; Amarendra Mikkilineni¹; Guixue Yu¹; Ximao Wu¹; Zhengxiang Gu¹; Natesan Murugesan¹; Bruce A. Ellsworth¹; Annapurna Pendri¹; Philip Sher¹; Gang Wu¹; Yeheng Zhu¹; Doree Sitkoff²; Liya Kang³; Yifan Yang³; Ning Lee³; Mary Jane Cullen³; William Keim³; Mary Ann Pelleymounter³; Paul Stetsko⁴; Gerry Everlof⁴; Olafur Gudmunsson⁴; Susan Johnghar⁴; Steven Wu⁴; Asoka Ranasinhe⁴; Wenying Li⁴; Kamelia Behnia⁴; Kenneth E. Carlson³; William R. Ewing¹. (1) Department of Metabolic Disease Chemistry, Bristol-Myers Squibb Research and Development, Princeton NJ 08543-5400, United States (2) Department of Computer Assisted Drug Design, Bristol-Myers Squibb Research and Development, Princeton NJ 08543-5400, United States (3) Department of Metabolic Disease Biology, Bristol-Myers Squibb Research and Development, Princeton NJ 08543-5400, United States (4) Department of Preclinical Candidate Optimization, Bristol-Myers Squibb Research and Development, Princeton NJ 08543-5400, United States

Pharmacologic blockade with CB1 (cannabinoid-1 receptor) antagonists results in hypophagia and decreased body weight in animal models. These observations have stimulated the search for potent and selective CB1 antagonists as a treatment for obesity. Several CB1 antagonists have demonstrated sustained weight loss in obese patients. Unfortunately, the long term safety profiles, e.g. the risk of psychiatric side effects, have halted the development of many centrally acting CB1 antagonists. However, there is continuing interest in exploring the CB1 blockage mechanism for therapeutic applications through other approaches, including the peripheral system. As part of a program to identify novel antagonists with improved CB1 in vitro and in vivo potency, as well as high selectivity for CB1 vs CB2 receptor, we designed and generated a series of novel 5,6-fused bicyclic (triazolopyridazine) templates by conformationally constraining the pyrazine carboxamide. The synthesis, SAR and pharmacology of the triazolopyridazine template based CB1 antagonists will be presented.

MEDI 351

Discovery of a new class of small molecule ROMK blockers for the treatment of hypertension

Haifeng Tang, *haifeng_tang@merck.com*; Yan Yan; Reynalda deJesus; Nardos Teumelsan; Yuping Zhu; Shawn Walsh; Aurash Shahripour; Ha Sookhee; Karen Owens; Brande Thomas-Fowlkes; John Felix; Jessica Liu; Martin Kohler; Birgit Priest; Timothy Bailey; Richard Brochu; Maria Garcia; Gregory Kaczorowski; Magdalena Alonso-Galicia; Sophie Roy; Lihu Yang; Sandy G Mills; Kathleen Sullivan; Alexander Pasternak. Merck Research Labs, Rahway New Jersey 07065, United States

Hypertension, also known as high blood pressure, is a serious chronic health problem. Persistent hypertension is one of the risk factors for stroke, myocardial infarction, heart failure, arterial aneurysm, and is also a leading cause of chronic kidney failure. Although a large number of treatments are available, many patients fail to achieve adequate blood pressure control and physicians commonly prescribe combination therapies. Among the existing antihypertensive agents, thiazide diuretics remain the second most widely prescribed class despite liabilities such as hypokalemia. The Renal Outer Medullary Potassium channel (ROMK, Kir1.1) is involved in salt reabsorption in the kidney. Human genetics suggested that ROMK blockers could be used as novel diuretic/natriuretic agents with reduced liabilities over the currently used diuretics. Genetic ablation of ROMK in rodents also supports these expectations. Thus, selective ROMK blockers are expected to be superior diuretics for the treatment of hypertension. This presentation will disclose a new class of selective small molecule ROMK blockers discovered from a High Throughput Screening (HTS) campaign. Basic SAR of this lead class will be discussed. Medicinal chemistry efforts leading to improvement of off-target selectivity and PK properties in preclinical species will be detailed.

MEDI 352

Discovery and optimization of potent and selective tissue factor/factor VIIa inhibitors

Shinsuke Hirota¹, *s-hirota@hhc.eisai.co.jp*; Richard Clark¹; Fumiyoshi Matsuura¹; Kazunobu Kira¹; Hiroshi Azuma¹; Tadashi Nagakura¹; Tatsuo Horizoe¹; Kimiyo Tabata¹; Kazutomi Kusano¹; Takao Omae¹; Atsushi Inoue¹; David Critchley². (1) Tsukuba Research Laboratories, Eisai Co., Ltd., Tsukuba-shi Ibaraki 300-2635, Japan (2) Department of Scientific Operations & Clinical Support, Eisai Product Creation Systems, Hatfield, United Kingdom

The blood clotting mechanism has been classified into two pathways, the "intrinsic clotting pathway" which begins with activation of factor XII (FXII) upon contact with negative charged substances, and the "extrinsic clotting pathway" which is activated by tissue factor (TF) and factor VII (FVII). Since the pathology of thrombosis onset is associated with specific expression of TF, it has been suggested that extrinsic clotting is

of major importance. Compounds that inhibit clotting factor VIIa, which is furthest upstream in the extrinsic clotting pathway of the clotting cascade, are thought to have potential use as therapeutic and/or prophylactic agents for diseases associated with thrombus formation, such as thrombosis, in which the extrinsic clotting mechanism plays a part. Here, we will describe the discovery of potent and selective triazolone derivatives as TF/FVIIa inhibitors. We will illustrate the synthesis and structure-activity relationships of the series and present the results of a human micro dosing study.

MEDI 353

Nano-sensors for apoptosis detection in atherosclerotic plaques

Ellen Broering, *ebroerin@uga.edu*; **Shanta Dhar**, *Department of Chemistry, University of Georgia, Athens Georgia 30602, United States*

Nano-sensors for Apoptosis Detection in Atherosclerotic Plaques Ellen Broering and Shanta Dhar* *Department of Chemistry, The University of Georgia, Athens, GA 30602 Email: ebroerin@uga.edu* Atherothrombotic vascular disease is responsible for more deaths than any other disease in the industrialized world. Although molecular-genetic approaches have identified arterial-wall targets, most approaches cannot be tailored to oral medications or to consistent therapy. Apoptosis of macrophages and smooth muscle cells along the arterial wall serves as a target for detection of plaque vulnerable to embolism. The anionic phosphatidylserine (PS) on the external membrane is one of the earliest signs of apoptosis and can be detected prior to a thrombotic event. To detect atherosclerotic evidence noninvasively, we began constructing a long-circulating nanoparticle platform, which can selectively target macrophages and sense apoptosis. We encapsulated MRI active iron oxide nanocrystals in a core of poly(D,L-lactic-co-glycolic acid)-*b*-poly(ethylene glycol) (PLGA-*b*-PEG). The nanoparticle surface was modified by macrophage targeting mannose, PS-targeting peptides, and Zn²⁺ binding domains, which can bind the PS. The utility of these nano-constructs in the diagnosis of atherosclerosis will be discussed.

MEDI 354

Cholesterol-derived novel anti-apoptotic agents on the structural basis of ginsenoside Rk1

Hongchan An¹, *godofks0@snu.ac.kr*; **Sujin Lee**¹; **Sony Maharjan**²; **Kyeojin Kim**¹; **Nam-Jung Kim**¹; **Hyun-Jung Cho**²; **Young Taek Han**¹; **Young-Guen Kwon**²; **Young-Ger Suh**¹.
(1) *College of pharmacy, Seoul National University, Seoul, Republic of Korea* (2) *Department of Biochemistry, Yonsei University, Seoul, Republic of Korea*

It has been known that vascular endothelial cell (VEC) apoptosis can induce an alteration in the integrity of vessels and the function of endothelium. Therefore, apoptosis inhibition has been considered as a new approach for treatment of vascular disorder. Our efforts for development of the potent anti-apoptotic agents have driven

discovery of ginsenoside Rg3 and Rk1, which exhibit potent anti-apoptotic activity in human umbilical vein endothelial cell (HUVEC) lines. However, instability of Rk1 and the extract process-dependent composition of ginsenosides limited studies on biological functions and underlying mechanisms of their biological activities. Based on our preliminary studies, we attempted to develop novel and structurally simplified VEC apoptosis inhibitors by introducing the carbohydrate equivalents. In addition, we selected cholesterol scaffold to substitute for the protopanaxadiol backbone of Rk1 in terms of structural similarity and ready accessibility. Taking together these, we have conducted design and synthesis of a series of cholesterol analogues.

MEDI 355

Discovery of novel polyamidoamine (PAMAM) dendrimer conjugated A₃ adenosine receptor agonist ligand as a cardioprotective agent

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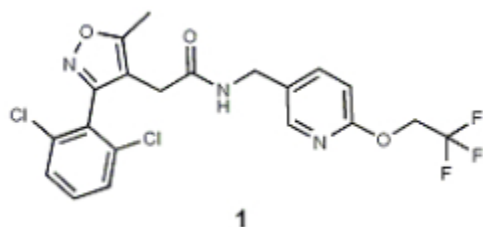
Adenosine released during myocardial ischemia mediates cardioprotective preconditioning. The chemical and biological properties of multivalent drugs bound to nanocarriers may differ greatly from those of the corresponding monomeric agents. Multivalent nucleoside conjugates have been synthesized from poly(amidoamine) (PAMAM) dendrimeric polymers, and their effects in rat primary cardiac cell cultures and in an isolated heart model were investigated. Three conjugates of A₃ adenosine receptor (AR) agonists, chain-functionalized at the C2 or N⁶ position, were cardioprotective, with greater potency than the monomeric agonist Cl-IB-MECA, and protection was blocked by an A₃AR antagonist. Multivalent amide-linked MRS5216 (selective for A₁ and A₃ARs) and triazole-linked A₃AR-selective MRS5246 and MRS5539 (optionally with fluorescent label) protected ischemic rat cardiomyocyte cultures and isolated hearts with improved infarct size, rate of pressure product, and rate of contraction and relaxation (p<0.05 vs. controls). Thus, strategically derivatized nucleosides tethered to biocompatible polymeric carriers display enhanced cardioprotective potency via activation of the A₃AR on surface of cardiomyocytes.

MEDI 356

Phenyl isoxazole voltage-gated sodium channel blockers: Structure and activity relationship

Istvan Macsari, istvan.macsari@astrazeneca.com; Lars Sandberg; Yevgeni Besidski; Yiva Gravenfors; Tobias Ginman; Johan Bylund; Tjerk Bueters; Per I. Arvidsson. CNSP iMed Science, AstraZeneca Research and Development, Sweden

Blocking of certain sodium channels is considered to be an attractive mechanism to treat chronic pain conditions. Phenyl isoxazole carbamates were identified as potent and selective Na_v1.7 blockers. Structural analogues, both carbamates, ureas and amides, were proven to be useful in establishing the structure activity relationship and improving ADME related properties. Amide **1** showed a good overall in-vitro profile, that translated well to rat in-vivo PK.



Na_v1.7 pIC₅₀ 6.75
 Na_v1.5 pIC₅₀ <4.48
 clogP 3.79
 hERG pIC₅₀ <4.58
 Solubility 36 µM

MEDI 357

Discovery of a clinically useful alkyl amine renin inhibitor

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Structure guided optimization of a series of non-peptidic alkylamine renin inhibitors allowed the rational incorporation of additional polar functionality into the previous lead inhibitor series. Replacement of the cyclohexylmethyl group occupying the S1 pocket with a (R)-3-(tetrahydropyranyl)methyl group and utilization of a different attachment point improved the selectivity of the compounds, leading to the identification of clinical candidate VTP-27999. This compound demonstrated excellent selectivity over related and unrelated targets, >15% oral bioavailability in three species, oral efficacy in a dTGR model of hypertension and bioavailability in human.

MEDI 358

Synthesis and antioxidant activity of carbonate co-drugs

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The aim of this project was to synthesize new antioxidant compounds for use as topical agents to protect the skin against oxidative damage caused by ultraviolet radiation. Co-drugs derived from tocopherol (TOC) and lipoic acid (LA), were prepared by coupling lipol (derived from reduction of lipoic acid) to chloroformates of TOC. Co-drugs were subjected to metabolic and chemical hydrolysis and hydrolysis products were quantified by HPLC. Antioxidant activity of the co-drugs was determined by measuring inhibitory

potency of the co-drugs on lipid peroxidation. Compounds were prepared in good yield (42-66%). Carbonate co-drugs hydrolyzed in the presence of enzyme as exhibited by a decrease in co-drug concentration and a concurrent increase in concentration of lipol and TOC, but were stable in the absence of enzyme. Hydrolyzed co-drugs inhibited lipid peroxidation to a greater extent than TOC or lipol alone, suggesting the antioxidant activity is synergistic.

MEDI 359

Binding of hydrophobic side chains in the S2' pocket of Thermolysin: Is it entropic or enthalpic driven binding?

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The entropy-driven hydrophobic effect is one of the major driving forces for ligand-macromolecule binding. The binding thermodynamic parameters, and affinity, of a series of thermolysin phosphoramidate inhibitors were evaluated wherein a range of hydrophobic side chains were present for interacting with the S2' pocket. The results showed that favorable entropy changes dominate binding when the ligand hydrophobic groups are large (e.g. isobutyl and benzyl) but favorable enthalpy dominates when the hydrophobic side chains are small (e.g. Me and Et). The cause of this enthalpy-driven binding is attributed to the formation of stronger H-bonds among the water molecules hydrating the unburied portion of the smaller hydrophobic groups in the ligand-enzyme complex. The reinforcement of the H-bond networks by the polar and H-bonding groups in the ligand-enzyme complex might be the cause of the enhanced H-bonding strength among the nearby water molecules.

MEDI 360

Preparation and evaluation of novel mechanism-based inhibitors of rhomboid proteases

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Rhomboids are a family of conserved intramembrane serine proteases which are known to participate in a number of diverse and important biological processes, ranging from possible roles in EGFR signaling to involvement in malarial parasite invasion of red blood cells. There is considerable interest in the structural and functional characterization of rhomboids and their potential validation as disease targets, and the

identification of small molecules that can inhibit or activate rhomboid activity would contribute significantly to this area of work. This poster will describe the application of a recently developed high-throughput screening approach to uncovering such molecules, and the identification of a series of β -lactams as potent and selective rhomboid inhibitors. Synthetic approaches to a range of analogues and key structure activity relationships will be presented, together with *in vivo* studies and observations on the likely mechanism of action.

MEDI 361

Inside the mind of a medicinal chemist

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The prioritization of compounds from large hit lists for further follow-up is an especially challenging task for medicinal chemists. During this step of drug discovery, multiple parameters such as synthetic accessibility, target specificity, solubility, and potential mutagenicity, in addition to assay activity, must be considered simultaneously. We sought to elucidate parts of the thought process of chemists during hit assessment by asking them to select chemical fragments (MW<300) that they would be willing to work with from a putative "hit" list. We subsequently applied data mining techniques to understand their choices. In all, twenty-seven chemists were asked to survey ~4,000 compounds. Bayes models were built using various combinations of properties (measuring ring topology, size, polarity, etc.) to try and understand which features were most important to individual chemists. We rigorously demonstrate that the majority of chemists only used 1-2 parameters during their fragment assessment, suggesting that medicinal chemists reduce a complicated problem into a more tractable one by focusing on a few parameters rather than on several. Interestingly, follow up questionnaires revealed that many chemists were unaware of what parameters dominated their decisions. The heretofore illusive "intuition" of medicinal chemists was further revealed by visually investigating individual models, and exposing subtle preferences such as combinations of functional groups or scaffold topology. We present our findings in the context of previous psychology studies that have been performed in the area of complex problem solving and decision theory, and discuss the implications on drug discovery.

MEDI 362

Computer LeadOpt assistance in medicinal chemistry

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In times of restructurings, more computation has to be accomplished by MedChems themselves. For software development, this prompts to acknowledge strong boundary conditions: - MedChem core expertise is *synthesis*, so the learning barrier for new software must be absent, and results must be delivered in seconds. - MedChems are "pattern recognizers" (C. Lipinski), so good *visualization* is key - especially in 2D. - We all need to *communicate* to colleagues and bosses, so software must generate graphics, tables/reports with high aesthetics and seamlessly integrate into Office tools etc. Several years of research have now addressed these issues, and we are now ready to present a collection of tools we think are of high interest to the MedChem personnel. The software is a monolithic suite that not only supports drag and drop of mol2, sdf, pdb files, but also lets users drag result 2D and 3D graphics into PowerPoint, Word etc. with a single click. Novel computational tasks included are: 1. Desolvation-respecting *affinity estimation* ("Hyde") with visualization of energy issues in compounds. 2. *Scaffold replacement* engine ("ReCore") that - within seconds - gives proposals for iterative optimization respecting pharmacophores and/or synthesis vectors. 3. 2D protein-ligand display ("PoseView" which was recently also linked to the PDB website). 4. Protein preparation which resolves crystallographic ambiguities such as H-positions. Experience in several big pharmas revealed that the time won can be re-invested in core MedChem tasks. We will showcase example workflows highlighting successes plus take a glance at the science behind.

MEDI 363

Effective use of in-silico tools in lead optimization

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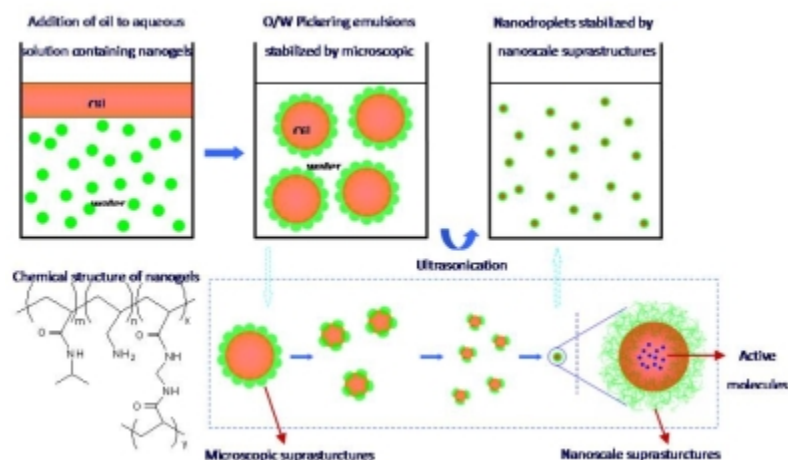
Despite constant advances in QSAR field, computational approaches in general still fail to meet the expectations. In this work we attempt to re-assess the role of various in-silico tools in building an effective lead optimization strategy. From the modeling perspective the emphasis is put on the mechanistic interpretations utilizing the most basic physicochemical characteristics of the compounds, e.g., lipophilicity, size, ionization, etc. The phenomenon of local 'anomalies' – the so-called 'activity cliffs' – is also covered providing suggestions for the statistical methods (pairwise QSAR) suitable to resolve such issues. Automated Hansch and Free-Wilson type analysis (Auto-SAR approach) is presented as a viable solution to include target affinity data in the analysis, potentially suggesting most promising candidates. Finally the potential of various in-silico techniques in the evaluation of other lead optimization aspects, such as synthetic feasibility or patentability prospects is overviewed.

MEDI 364

Deformable nanogels into nanoscale suprastructures and their application in nanomedicine

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Assembly of nanoparticles as interfacial stabilizers at oil-in-water (O/W) interfaces into microscopic suprastructures for stabilizing Pickering emulsions is an intriguing focus in the fields of chemical industry and material sciences. However, it is still a major challenge to assemble these nanoscale suprastructures for the applications in medicine. We show that it is possible to fabricate the nanodroplets by assembling highly deformable nanogels into the nanoscale suprastructures. The hydrogen bonding interaction between the nanogels at the O/W interface are possibly responsible for the stabilization of the nanoscale suprastructures. The nanoscale suprastructures are further employed to stabilize the paclitaxel-loaded nanodroplets, which are found to provide sustained release of the drug, prolonged in vivo blood circulation, and enhanced tumor growth inhibition. This approach provides a novel universal strategy to fabricate nanoscale suprastructures for stabilizing nanodroplets with built-in payloads using deformable nanoparticles and displays a promising potential in nanomedicine.



MEDI 365

Fast and efficient purification of lipids and lipid-based compounds using flash chromatography

Melissa J Wilcox, melissa.wilcox@grace.com; Kiran Chodavarapu; Kathy Lawrence; Kimberly Wolfson. Department of Technology, Grace Davison Discovery Sciences, Deerfield IL 60015, United States

Lipids play a major role in biological functions due to their presence in all cells. Lipids are usually hydrophobic in nature, soluble in organic solvents, and contain nonpolar fatty acid groups. Purifying complex mixtures containing non-chromophoric or poorly chromophoric compounds like lipids can be difficult. Traditional ultraviolet (UV) detection fails to detect lipids and impurities that are present at low levels or lack chromophores, requiring a 'collect all' approach that can add significant time to the purification process.

This work demonstrates purification of lipid-based compounds (fatty acids, sterols, stearins, and others) that are weakly chromophoric using a Reveleris® flash chromatography system. With RevealX™ detection technology in the Reveleris® System, chemists can purify lipid-based compounds that are non-chromophoric with speed and high purity. A variety of Reveleris cartridge chemistries can be applied to maximize separation and purity of complex lipid mixtures.

MEDI 366

Efficient purification of small peptides using flash chromatography with RevealX™ detection technology

Melissa J Wilcox, *melissa.wilcox@grace.com*; *Kiran Chodavarapu*; *Kathy Lawrence*; *Kimberly Wolfson*. *Grace Davison Discovery Sciences, Deerfield IL 60015, United States*

Newly discovered peptide sequences provide tools in understanding the functions of biological systems and support for novel drug development. Purification of synthetic peptides is an essential step in the drug discovery process. It is traditionally done by preparative chromatography, which can be expensive and time consuming. Flash chromatography is a fast and cost-efficient approach to purify synthetic peptides and other small molecules. This work demonstrates purification and recovery of small peptides using a Reveleris® Flash Chromatography System with RevealX™ technology. Using the Reveleris® flash chromatography system combined with high capacity Reveleris® cartridges streamlines purification of small peptides.

MEDI 367

WITHDRAWN

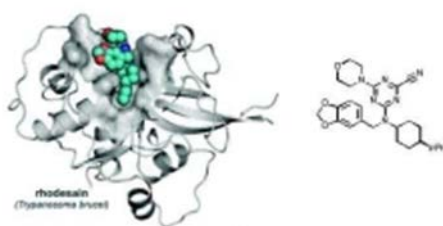
MEDI 368

Potent and selective inhibition of cysteine proteases from *Plasmodium falciparum* and *Trypanosoma brucei*

Veronika Ehmke¹, *veronika.ehmke@org.chem.ethz.ch*; *Matthias Rottman*²; *Reto Brun*²; *Tanja Schirmeister*³; *François Diederich*¹. (1) *Laboratory of Organic Chemistry, ETH Zurich, Switzerland* (2) *Swiss Tropical and Public Health Institute, Switzerland* (3) *Institute of Pharmacy, University of Würzburg, Germany*

Malaria and African sleeping sickness, caused by the parasitic protozoa *Plasmodium falciparum* and *Trypanosoma brucei*, are among the most severe tropical diseases representing health issues in the developing world.^[1] The emergence of multidrug-resistant parasite strains, in addition to limitations of chemotherapies, demand the development of new drugs with novel mechanisms of action. *P. falciparum* and *T. brucei* offer several potential target enzymes, including a number of essential cysteine

proteases. Falcipain-2, a hemoglobinase of *P. falciparum*, and rhodesain, a cathepsin L-like hydrolase of *T. brucei*, emerged as targets for drug development since they exhibit crucial roles in the parasites' life-cycles. Based on X-ray crystal structures, we utilized computer-aided modeling to design drug-like molecules featuring a nitrile residue as electrophilic head group to covalently interact with the catalytic cysteine.^[2] With our structure-based design approach, we prepared functionalized triazine nitriles which were tested against falcipain-2 and rhodesain. Single-digit nanomolar activities were obtained for the designed ligands. Biological assays showed in most cases good selectivity against closely related human enzymes. Cell-based assays against the parasites revealed moderate *in vitro* activity. These results gave rise for detailed optimization studies which are currently ongoing.



MEDI 369

Designing isoform selective inhibitors of phosphoinositide 3-kinases

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Phosphatidylinositol 3-kinases (PI3K) hold significant therapeutic potential as novel targets for multiple diseases. The four closely related Class I isoforms have been implicated in cancer (α , β , δ), thrombosis (β) and various inflammatory and autoimmune disorders (γ , δ). A highly conserved active site presents researchers with a compelling challenge to develop isoform selective inhibitors able to limit off-target effects. Drawing on the current understanding of the mechanisms of isoform selectivity, we have sought to target regions of non-conserved residues through substitution and derivatisation of the non-selective inhibitor, ZSTK474¹. To date, we have been able to achieve significant changes in isoform selectivity through simple substitutions. The design, synthesis and activity of these inhibitors will be presented. (1) Yaguchi, S.; Fukui, Y.; Koshimizu, I.; Yoshimi, H.; Matsuno, T.; Gouda, H.; Hirono, S.; Yamazaki, K.; Yamori, T. Journal of the National Cancer Institute 2006, 98, 545.

MEDI 370

Structure activity relationship, in vitro and in vivo profile of JN403, a nAChR $\alpha 7$ selective agonist

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Several lines of evidence suggest that the nicotinic acetylcholine receptor $\alpha 7$ (nAChR $\alpha 7$) is involved in neuropsychiatric disorders like schizophrenia and Alzheimer's disease. By optimizing a quinuclidine carbamate scaffold, we have discovered a novel selective nicotinic acetylcholine receptor (nAChR) $\alpha 7$ agonist, JN403, (S)-(1-aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid (S)-1-(2-fluoro-phenyl)-ethyl ester. JN403 was evaluated in a number of *in vitro* systems of different species, at recombinant receptors using radioligand binding and signal transduction studies. JN403 has high affinity for human recombinant nAChR $\alpha 7$ ($pK_D = 6.7$) and stimulates calcium influx in GH3 cells recombinantly expressing the human nAChR $\alpha 7$ with a pEC_{50} of 7.0 and an E_{max} of 85 %. JN403 shows low binding activity at a panel of neurotransmitter receptors. JN403 rapidly penetrates into the brain after p.o. administration in mice and rats. In mice, JN403 facilitates learning/memory performance over a dose range of 1-3 mg/kg, s.c. JN403 shows anxiolytic-like properties in rats (10-30 mg/kg, p.o.) and the effects are retained after a 6 h pre-treatment period and following subchronic administration. In DBA/2 mice, JN403 restores sensory gating, both in anaesthetized and awake animals (50 mg/kg, s.c.). Altogether, the present set of data suggests that nAChR $\alpha 7$ agonists, and notably JN403, may be beneficial for improving learning/memory performance and restoring sensory gating deficits.

MEDI 371

Design, synthesis, and pharmacological evaluation of dihydrobenzofuran amide derivatives as γ -secretase modulators

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γ -Secretase modulators (GSMs) have emerged as a potential disease modifying treatment for Alzheimer's disease. While γ -secretase inhibitors (GSIs) block the cleavage of all γ -secretase substrates including Notch, which is important for cell differentiation, GSMs selectively alter the cleavage site of the amyloid precursor protein (APP) to reduce the formation of the neurotoxic peptides A β 42 and A β 40. As an intra-membrane cleaving aspartyl protease, γ -secretase presents a significant challenge for small molecule drug discovery. This is exemplified by the relatively high cLogP observed for compounds reported in the GSM patent literature. The alignment of potency, clearance, and brain penetration, while maintaining good physicochemical

properties to ensure an adequate therapeutic index has proven to be particularly challenging. This presentation will describe our efforts toward this goal, which have resulted in the discovery of centrally active GSM leads.

MEDI 372

Discovery of potent and selective inhibitors of Ataxia telangiectasia mutated and Rad3 related (ATR) protein kinase as potential anticancer agents

Jean-Damien Charrier, *jean-damien_charrier@vrtx.com*. Chemistry, Vertex Pharmaceuticals (Europe) Ltd, United Kingdom

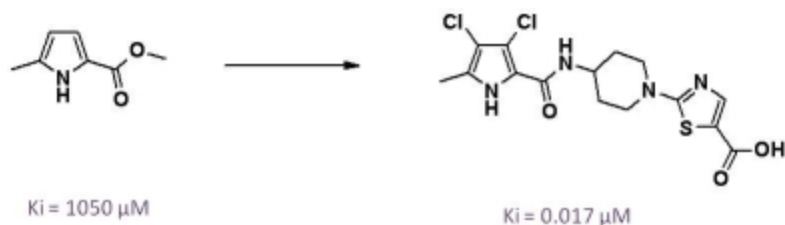
Exploiting genetic lesions in cancer that drive a reliance on druggable proteins for survival provides an opportunity to deliver safer anti-cancer drugs. Two related kinases, ATM and ATR, are key regulators of a critical survival pathway that responds to DNA damage. In normal cells, these kinases have an overlapping role. However, defects in ATM signaling pathway are common in cancer and could drive reliance on ATR for survival from DNA damage. Here, we describe the discovery of the first potent, selective and drug-like ATR inhibitors. We show that cancer cells with defects in ATM signaling pathway are markedly sensitized to the cytotoxic effects of DNA damaging agents by ATR inhibition. In stark contrast normal cells, with a functional ATM pathway, can tolerate ATR inhibition. These findings establish ATR inhibition as a novel and safe approach to dramatically increase the efficacy of many widely used DNA damaging drugs and ionising radiation.

MEDI 373

Synthesis of functionalized pyrroles as building blocks for novel inhibitors of bacterial DNA gyrase

Pamela J Hill, *pam.hill@astrazeneca.com*; Gregory S Basarab; Shanta Bist; Oluyinka Green; Sheila Hauck; Ken Hull; Brian Sherer. Infection Discovery, AstraZeneca, R&D Boston, Waltham MA 02451, United States

Bacterial DNA gyrase is a type II topoisomerase that is responsible for DNA topology during cell replication. Inhibitors of DNA gyrase block DNA synthesis and ultimately lead to cell death. Fragment based lead generation using NMR identified low molecular weight fragments that bind to the ATP binding site of bacterial DNA gyrase with millimolar affinity. Of the fragment hits, the pyrrole was chosen due to the hydrogen bonding motif and the opportunities for optimization. Chemistry was designed to achieve unique regioselective functionalizations of pyrrole fragments. A structure based drug design approach was used to elaborate fragments into lead compounds of novel pyrrolamide class with good antibacterial potency. Lead compounds demonstrated low nanomolar potency against the target with good physical properties and demonstrated efficacy in animal models.



MEDI 374

Synthesis and SAR analysis of a library of TSHR modulators

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Thyroid stimulating hormone (TSH), an α/β heterodimeric glycoprotein hormone, is secreted from the anterior pituitary gland and binds to the TSH receptor (TSHR). TSHR is mainly expressed in thyroid follicular cells, but is also found in the bone, brain, kidney, testis, endometrium, and immune system. A TSHR modulator could provide a valuable pharmacological tool for researchers interested in exploring this receptor and a small molecule antagonist has the potential to be used clinically for patients with Graves' disease. Recombinant human TSH (rhTSH, Thyrogen[®]) has been used in the follow-up of patients with thyroid cancer. A small molecule TSHR agonist could produce the same beneficial effects as rhTSH, but with greater ease of oral administration. Previously, a library of 73,180 compounds was screened at NCGC and a selective TSHR agonist was identified. SAR studies have led to the identification of a more potent TSHR agonist and new TSHR antagonists and inverse agonists.

MEDI 375

Progress toward the development of small molecule inhibitors of TLR-4 signaling

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It has been demonstrated that the heterodimerization of TLR4 (Toll Like Receptor 4) and the accessory protein MD2 is responsible for the up regulation of pro-inflammatory cytokines such as TNF- α and IL1- β through the activation of the NF- κ B signaling pathway. This TLR4 induced pro-inflammatory signaling has been implicated in a several autoimmune diseases as well as in sepsis, making TLR4 an interesting therapeutic target. Herein, we describe the identification, synthesis and biological

results for a series of small molecule inhibitors that exhibited effectiveness and selectivity for the modulation of the TLR4-mediated inflammation response. [Figure 1]

MEDI 376

Small molecule modulation of the Lysophosphatidic acid pathway in the treatment of neoplastic growth

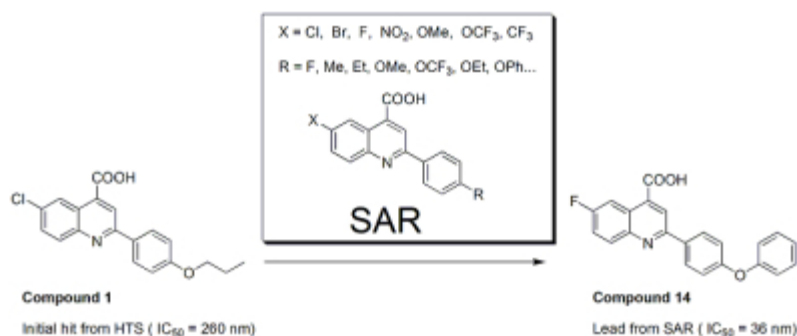
James E East¹, je5y@virginia.edu; Kevin R Lynch²; Timothy L Macdonald¹. (1) Department of Chemistry, University of Virginia, Charlottesville VA 22902, United States (2) Department of Pharmacology, University of Virginia, Charlottesville VA 22902, United States

Lysophosphatidic Acid (LPA) is an endogenous phospholipid signaling molecule implicated in a myriad of neoplastic disease states including breast and prostate cancer. LPA contributes to these diseases due its role in numerous biological processes such as angiogenesis, cell proliferation, migration and invasion. LPA is synthesized from lysophosphatidylcholine (LPC) by the Nucleotide Phosphatase/Pyrophosphatase 2 (NPP2) enzyme Autotaxin (ATX). Once synthesized by ATX, LPA goes on to act on one of five LPA Receptors (LPA1-5). These receptors are classical G-protein coupled receptors (GPCRs) that are responsible for Ca²⁺ mobilization and increasing MAP kinase and phosphatidylinositol biphosphate (PIP₂) pathway activities. Our labs have developed two small molecules derived from L-tyrosine: one, VPC8a202, that inhibits the synthesis of LPA while the other, VPC51299 blocks the signaling of the LPA1 and LPA3 receptors. These compounds are not only efficacious in *in vitro* studies but have been shown to reduce tumor size and metastasis *in vivo*.

MEDI 377

HTS and structure-activity based discovery of a novel class of 4-quinoline carboxylic acids with excellent anti-influenza activity

Priyabrata Das¹, priyabrata.das@utsouthwestern.edu; Liang Zhang²; Mirco Schmolke³; Yaming Wang⁴; Xiaoyi Deng⁵; Michael G. Roth¹; David E Lavy⁴; Adolfo Garcia-Sastre³; Margaret A Phillips⁵; Beatriz Fontura²; Jef de Brabander¹. (1) Department of Biochemistry, University of Texas Southwestern Medical Center at Dallas, Dallas TX 75390, United States (2) Department of Cell Biology, University of Texas Southwestern Medical Center at Dallas, Dallas TX 75390, United States (3) Department of Medicine, Mount Sinai School of Medicine, New York NY 10029, United States (4) Department of Pathology, New York University School of Medicine, New York NY 10016, United States (5) Department of Pharmacology, University of Texas Southwestern Medical Center at Dallas, Dallas TX 75390, United States



Influenza virus NS1 protein is a major pathogenic factor. NS1 inhibits host gene expression and antiviral response by down regulating host nuclear mRNA processing and export as well as signaling pathways involved in interferon response. As a result, novel inhibitors of NS1 protein are important for anti-influenza drug discovery. Our studies started with the identification of 4-quinoline carboxylic acid **1** (IC₅₀ = 260 nm) from a high throughput screen. Here, we describe the synthesis and in vitro evaluation of novel 4-quinoline carboxylic acid analogues to determine the structure-activity relationship. Replacement of the aromatic propyloxy substituent with a methyl, fluorine, 2-pyridyloxy, 3-pyridyloxy substituent resulted in significantly lowered antiviral activity, whereas replacement with a trifluoromethyloxy, phenoxy substituent increased potency in this assay. It was found that replacement of quinoline chlorine with hydrogen, fluorine and nitro group resulted in increased activity. These efforts have led the discovery of **14**, an extremely potent analogue with highest antiviral activity (IC₅₀ = 36 nm). We noticed that compound **14** and analogues are structurally related to brequinar, also a 4-quinoline carboxylic acid. Brequinar is a known inhibitor of human dihydroorotate dehydrogenase (DHODH), a key enzyme in the *de novo* biosynthesis of pyrimidines. Based on this information we tested **14** and analogues for their ability to inhibit recombinant human DHODH. This assay led to the discovery of the target enzyme for the anti-influenza activity as DHODH with compound **14** showing the best DHODH inhibitory activity.

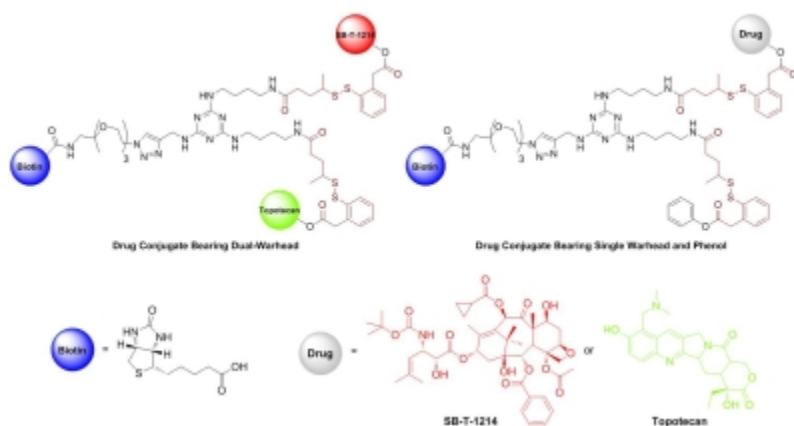
MEDI 378

Design, synthesis and biological evaluation of tumor-targeting drug conjugates bearing dual-warheads

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Combination therapy with single pharmacokinetics, obviously, has potential advantages over conventional protocol. Thus, we designed and synthesized a tumor-targeting drug conjugate bearing two different anticancer agents, SB-T-1214 and topotecan, as warheads. SB-T-1214 targets microtubules, while topotecan targets topoisomerase I in the nucleus. We have observed substantial synergy between these two agents in

certain cancer cells *in vitro*. Accordingly, a highly beneficial synergistic effect on efficacy is expected when these two agents are delivered to cancer cells simultaneously by a dual warhead conjugate via receptor-mediated endocytosis. In order to examine the anticipated synergy between two warheads in a fair manner, we also synthesized two other conjugates bearing the taxoid or topotecan as one warhead and phenol as a dummy warhead, using exactly the same scaffold as that of the dual warhead conjugate. The synthesis and biological evaluation of these novel tumor-targeting drug conjugates will be presented.

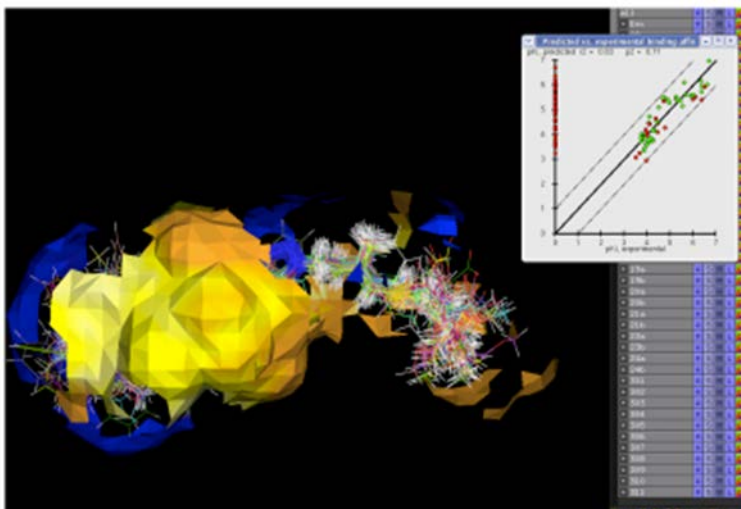


MEDI 379

Development and validation of a predictive quantitative structure-activity-relationship (QSAR) model for the TAB generation of isoprenylcysteine carboxylmethyl transferase (Icmt) inhibitors

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Icmt is the last downstream enzyme to perform post-translational modifications on Ras. Mutant Ras is implicated in 30% of all cancers and greater than 90% of all pancreatic cancers. Inactivating Icmt causes Ras to mislocalize and inhibits oncogenic signaling. Icmt is an enzyme that is embedded in the ER. There is no experimental or calculated structure for Icmt. In the absence of structural information, we have adopted a substrate-based approach and have synthesized a library of compounds that are nanomolar inhibitors of Icmt. To understand the inhibition requirements of this class of compounds, we have initiated a QSAR effort. Development of the QSAR model (using Raptor) has provided us with a predictive model with a R^2 of 0.83 and a predictive R^2 of 0.72



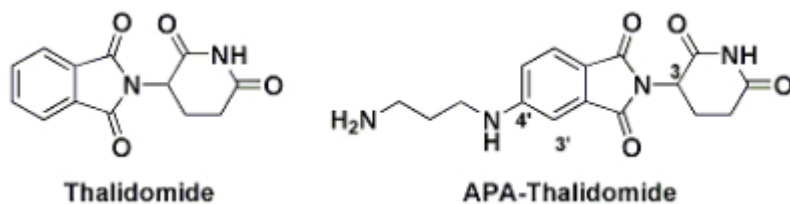
The model has successfully predicted activities of a few analogs. We are in the process of further evaluating the predictive power of the QSAR model by synthesizing analogs predicted by the model and evaluating them against Icmt.

MEDI 380

Thalidomide analogs reduce apoptosis in a PDT-induced apoptosis model

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Based on our previous results for neuroinflammation treatment, we investigated the potential anti-apoptotic activity of derivatives of APA-Thalidomide in a PDT-induced apoptosis model.



Compared to NAC, two analogues efficiently reduced ROS and singlet molecular oxygen mediated apoptosis. One of them was about twenty times more active than the reference antioxidant.

MEDI 381

Physicochemical and DMPK property calculations: How well can measured data be predicted?

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Calculation of physicochemical and DMPK properties of candidate molecules ahead of synthesis is becoming more widespread with the availability of predictive models. Commercial software is available to do predictions, and many companies have developed models using internal data. Which properties can be calculated accurately, and which ones remain problematic to forecast? Are commercially available models adequate, or must one develop their own models? How truly widespread is model usage, and what prevents models from being employed more effectively? This talk will cover available software and models, and touch on factors governing acceptance and usage of computational models by medicinal chemists. Considerations for developing internal models versus using commercial software will be described. An example of a deployment of a DMPK model to chemists' desktops will be presented, and its subsequent impact on drug properties across the organization will be described.

MEDI 382

QSAR ADMET models that stand the test of time

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Quantitative structure-activity models have been core computational chemistry tools since their popularization by Hansch and Fujita in the early 1960's. For many years they were limited in their applicability to congeneric series and small datasets. Research in the 1990's highlighted the potential to "tune-down" or "tune-out" ADME (absorption, distribution, metabolism, elimination) –linked development attrition by prudent ADME screening in Discovery. The growing ADME datasets, and the fact that many of these endpoints were more bulk-property controlled, rather than structure-class specific, provided fruitful opportunities for computational chemistry to use QSAR tools to build "global" cross project ADME QSAR models. These have been very successful in building-in good ADME properties into molecules at the compound design-stage. More recently a similar focus on toxicology has provided tox-based QSAR models, allowing us to add "T" to the acronym to broaden the study to ADMET models. But QSAR's are empirical models that only offer the potential to encode information provided within the description of the training set. Predictions can only confidently be made when the prediction molecule is within the domain of applicability of the original model. But molecular design evolves within a project, as data feedback guides compound design, and therefore the project chemical space tends to grow away from the original QSAR model. This poses a problem for QSAR models. We will describe our own exploration of the relationship between prediction quality and time, for a number of representative

ADMET endpoints in Discovery projects. We will describe how we have identified robust machine learning techniques, and used these together with informatics automation to build, and update “global” cross-project and “local” series-specific ADMET QSAR models that can stand the test of time.

MEDI 383

Use of azaheterocycles to modulate metabolic rates of drug metabolism

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Many new potential drugs have nitrogen in heterocyclic rings. The incorporation of nitrogen may be important for the pharmacophore, or the physical characteristics of the molecule. Incorporation of nitrogen can also have profound effects on the pharmacokinetics of a molecule. Three separate computational approaches to understanding the effects of nitrogen on metabolism will be presented. The first two have to do with modeling nitrogen-heme-iron interactions in cytochrome P450 enzymes and the third with predicting regioselectivity and rates of aldehyde oxidase mediated reactions.

MEDI 384

In silico toxicity assessment, back to the future

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As the pace of pharmaceutical drug discovery accelerates and greater numbers of preclinical candidates are identified by high throughput screening and synthetic methods, the demand for safety assessment resources has increased. As most *in vitro* toxicology assays are, at best, medium throughput, it is apparent that rapid *in silico* assessment methods must be developed and validated for use in early discovery. Regulatory agencies have long been at the forefront of utilizing computational tools to aid in the analysis of small molecules. Methods to effectively utilize all of the public and proprietary data available to extract meaningful information must be developed and validated. This discussion will present a series of examples to illustrate a) the different approaches used to model various preclinical toxicity endpoints, b) the pitfalls associated with relying solely on statistics to guide assessment of a molecule, and c) tools for capturing the metadata associated with risk analysis.

MEDI 385

PK profiles from your desktop: Predicting clinical pharmacokinetics

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Quantitative human pharmacokinetic (PK) predictions play a critical role in assessing the quality of potential oral drug candidates where clearance, volume of distribution, bioavailability and the plasma-concentration-time profiles are the desired endpoints. While many methods for conducting predictions utilize in vivo data, predictions can be conducted successfully from in vitro or in silico data, and modeling and simulation. This approach is facilitated using GastroPlus™ which has been reported to accurately predict the absorption and PK profile of small drug-like molecules. Herein, case studies are described where GastroPlus™ modeling and simulation was employed using in vitro and in silico data to predict human PK. The results obtained provided key information that led to decisions on either dose selection, chemistry strategy to improve lead matter or clinical protocol design, thus demonstrating the value of modeling and simulation in both early discovery and exploratory development for predicting absorption and pharmacokinetic profiles.